Regio- and diastereo-selectivity in directed aldol reactions of cyclopent-2-enone and but-2-en-4-olide

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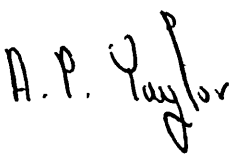
REGIO- AND DIASTEREO-SELECTIVITY IN DIRECTED ALDOL REACTIONS OF CYCLOPENT-2-ENONE AND BUT-2-EN-4-OLIDE

submitted by ANTHONY PHILIP TAYLOR

for the degree of Doctor of Philosophy

of the University of Bath

1988



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To my Mother

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Finally, I would like to thank my friends and colleagues at the University for making my stay at Bath a most enjoyable one.

ABSTRACT

The first part of this thesis involves a systematic investigation of the regio- and diastereo-selectivity of the directed aldol reaction of the lithium, silyl and zirconium dienolates of cyclopent-2-enone. When the reactions were performed under kinetic conditions, 5-substituted cyclopent-2-enone aldols were produced. The relative stereochemistry of the aldol products was determined and transition state models have been proposed to explain the regio- and diastereo-selectivity of the addition reactions. A brief study of the stereo-selectivity of the aldol reaction of the lithium dienolate of cyclopent-2-enone with the chiral aldehyde (2R)-2,3-*O*-isopropyl-ideneglyceraldehyde was also undertaken.

The 5-substituted cyclopent-2-enone aldols have been converted to 5-(1'-hydroxyalkyl)pentan-5-olides and 5-(1'-hydroxy-alkyl)pent-2-en-5-olides by methodology which allows their stereochemistry to be controlled to a high degree.

The second part of this thesis involves a complementary study on the regio- and diastereo-selectivity of the directed aldol reaction of the silyl dienolate of but-2-en-4-olide. Lewis acid- and fluoride ion-mediated aldol reactions under kinetic and thermodynamic conditions were found to be regio-specific, only 4-substituted but-2-en-4-olides being formed. However, when lanthanide reagents were used to mediate the additions under equilibrating conditions, the regioselectivity of the reaction changed and 2-substituted but-2-en-4-olides were the major products. Several transition state models have been proposed to explain the regio- and diastereo-selectivity of these aldol reactions. The aldol reaction of the lithium dienolate of but-2-en-4-olide has also been investigated.

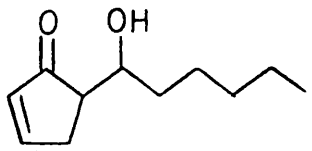
ABBREVIATIONS

Ac	acetyl
atm	atmosphere
b.p.	boiling point
i-Bu	*iso*-butyl
n-Bu	butyl
t-Bu	*tert*-butyl
Bz	benzoyl
C.I.	chemical ionisation
Cp	cyclopentadienyl ligand
DBU	1,8-diazabicyclo[5.4.0]undec-5-ene
DCM	dichloromethane
DIBAL-H	di-isobutylaluminium hydride
DMPA	4-*N*,*N*-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone
EE	ethoxyethyl
E.I.	electron impact
eq	equivalent
Et	ethyl
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octandionato
g.l.c.	gas-liquid-chromatography
h	hour
HMPA	Hexamethylphosphoric triamide
HMPT	hexamethylphosphorus triamide
Hz	Hertz
i.r.	infrared
J	coupling constant
LA	Lewis acid
LDA	lithium di-isopropylamide

MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	methoxymethyl
mg	milligram
min	minute
mmol	millimole
m.p.	melting point
m.s.	mass spectrum
m/z	mass to charge ratio
n.m.r.	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
ppm	parts per million
i-Pr	*iso*-propyl
PPTS	pyridinium *para*-toluenesulphonate
R_f	retention index for thin layer chromatography
RT	room temperature
TBAF	tetrabutylammonium fluoride
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
THP	tetrahydropyran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl (*para*-toluenesulphonyl)

Nomenclature and Numbering Systems

Examples of the nomenclature and numbering system used throughout this thesis are illustrated below, denoted with an asterisk, together with examples of alternative nomenclature commonly encountered in the literature.



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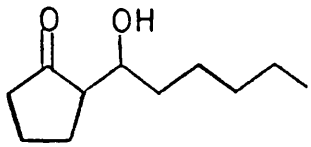
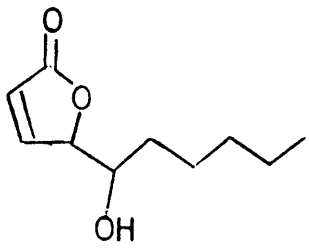


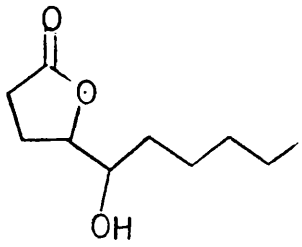
2-(1'-Hydroxyhexyl)cyclopentanone*



4-(1'-Hydroxyhexyl)but-2-en-4-olide*

5-Hydroxydec-2-en-4-olide

5-(1'-Hydroxyhexyl)-2-(5H)-furanone

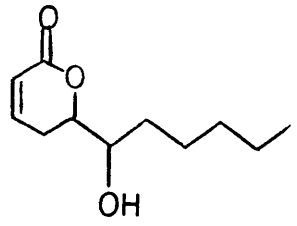


4-(1'-Hydroxyhexyl)butan-4-olide*

5-Hydroxydecan-4-olide

5-(1'-Hydroxyhexyl)tetrahydrofuran-2-one

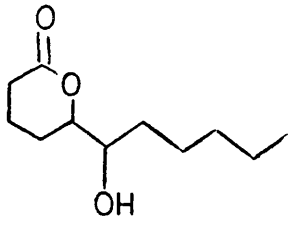
5-(1'-Hydroxyhexyl)oxacyclopentan-2-one



5-(Hydroxyhexyl)pent-2-en-5-olide*

6-Hydroxyundec-2-en-5-olide

6-(1'-Hydroxyhexyl)-5,6-dihydropyran-2-one

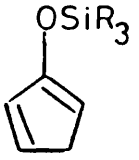


5-(1'-Hydroxyhexyl)pentan-5-olide*

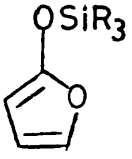
6-Hydroxyundecan-5-olide

6-(1'-Hydroxyhexyl)-3,4,5,6-
tetrahydropyran-2-one

6-(1'-Hydroxyhexyl)oxacyclohexan-2-one



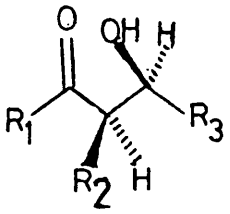
2-(Trialkylsiloxy)cyclopenta-1,3-diene*



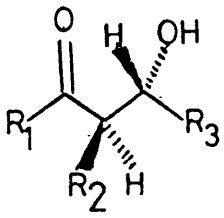
2-(Trialkylsiloxy)furan*

Stereostructural Notation

Systems of nomenclature used to describe compounds possessing two adjacent asymmetric centres can be confusing. Originally compounds such as A and B were referred to as *erythro* and *threo* diastereoisomers respectively. This nomenclature stemmed from the original Fischer projections for erythrose and threose sugars.



A

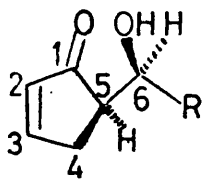


B

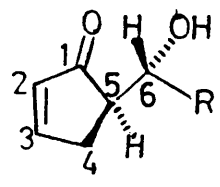
Although useful, this stereostructural notation is incorrect for most structural permutations of R_1 and R_3. In an attempt to clarify this situation, Masamune[1] and Heathcock[2] have proposed the use of the stereostructural descriptors *syn* and *anti*. If the main chain of the molecule, that is, the chain that contains the two asymmetric carbons is drawn in an extended zig-zag fashion, then the *syn* diastereoisomer is the one in which both substituents on the asymmetric carbons project towards or away from the viewer. The advantage of the *syn*:*anti* convention is that it is easily visualised and can be used readily to specify the relationship between any two asymmetric carbons, whether or not they are vicinal. Throughout this thesis the *syn*:*anti* nomenclature has been used in the following sense:

Cyclopent-2-enone aldols

The zig-zag chain is $-^{1}CO-^{5}CH-^{6}CH-R$ and the substituents at the asymmetric carbons are $^{4}CH_2$ and OH.



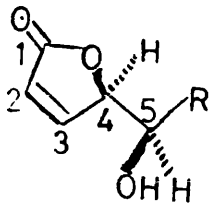
syn aldol



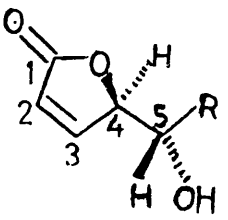
anti aldol

But-2-en-4-olide aldols

The zig-zag chain is $-^{3}CH-^{4}CH-^{5}CH-R$ and the substituents at the asymmetric carbons are OH and OCO.

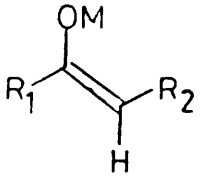


syn aldol

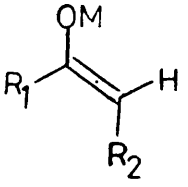


anti aldol

With regard to enolate stereostructural nomenclature, enolates possessing a *syn* stereochemical relationship between substituent R_2 and oxygen substitutent OM will be referred to as Z-enolates. In a similar fashion,enolates possessing an *anti* stereochemical relationship between R_2 and OM will be designated as E-enolates.



Z-enolate



E-enolate

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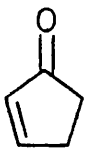
INTRODUCTION

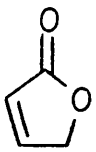
CHAPTER 1

Introduction

The objective of the research programme was to investigate the regio- and stereo-selectivity of the aldol reaction of cyclopent-2-enone (1) and its heterocyclic oxygen analogue but-2-en-4-olide (2).



(1)



(2)

There have been several reports on the aldol chemistry of derivatives of both systems (see sections 2.1 and 3.1), but none of these has involved a detailed or systematic examination of the stereochemistry of the product and factors which control the regio- and stereo-chemistry. In this thesis, these points have been examined and our findings are described in Chapters 2 and 3.

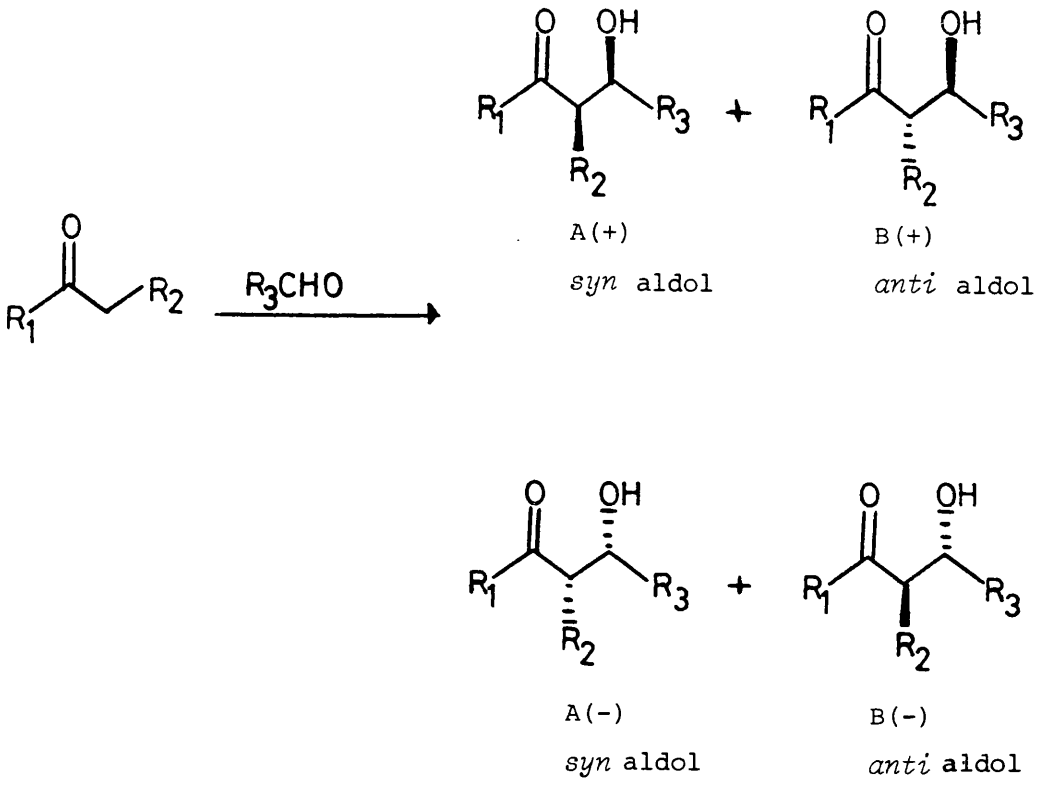
Since the majority of the project work was concerned with aldol reactions, it is pertinent to review recent advances in the control of the stereochemistry of this important reaction.

1.1 The Stereoselective Aldol Reaction

"Nature, it seems, is an organic chemist having some predilection for the aldol and related condensation....."

J.W. Cornforth

The aldol reaction is among the most important methods of forming carbon-carbon bonds.[3] The addition of a prochiral enolate to a prochiral aldehyde can lead to the formation of four stereoisomers (Scheme 1).



Scheme 1

Consequently, there are two stereochemical aspects associated with the reaction. The first deals with relative stereochemical control, or 'simple diastereoselectivity', [A(±) *v* B(±)], and the second deals with absolute stereochemical control for a given stereoisomer enantioselectivity or 'diastereofacial selectivity' [A(+) *v* A(-) or B(+) *v* B(-)].

In the last twenty years, extensive research has focussed on methods of controlling both forms of aldol stereoselectivity. Considerable progress has been achieved and some of the more important findings are briefly reviewed in this chapter. For a

more detailed discussion of the topic, the reader is referred to several excellent reviews.[4] Aldol reactions can be performed under conditions of kinetic control (low temperature, short reaction times) or thermodynamic control (equilibration conditions). In general, better stereoselectivity has been achieved under conditions of kinetic control.

1.2 Simple Diastereoselectivity under Kinetic Control

When an aldol reaction is carried out under conditions of kinetic control, the stereochemical outcome of the reaction depends on several factors. These include the nature of the enolate counterion and its attached ligands, the substituents attached to the enolate, the substituent attached to the aldehyde and the solvent employed. Of these factors, the most influential is the nature of the enolate counterion and thus, this discussion of simple diastereoselectivity has been organised with this in mind.

1.2.1 Groups I → III metal enolates

For preformed enolates of Groups I → III metals, the stereoselectivity of the aldol reaction is governed by two factors:

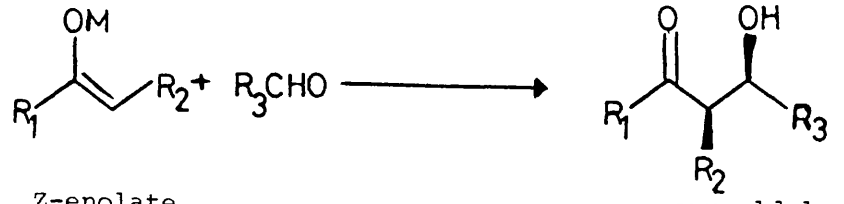
(a) the geometry of the enolate; and

(b) the nature of the substituents R_1 and R_2 attached to the enolate.

In general, Z-enolates form *syn* aldols and E-enolates form *anti* aldols (Scheme 2). Simple diastereoselectivity of Groups I → III metal enolates is best when R_1 is sterically demanding and R_2 is sterically subordinate. In addition to this general rule for simple diastereoselectivity, several other trends have emerged:

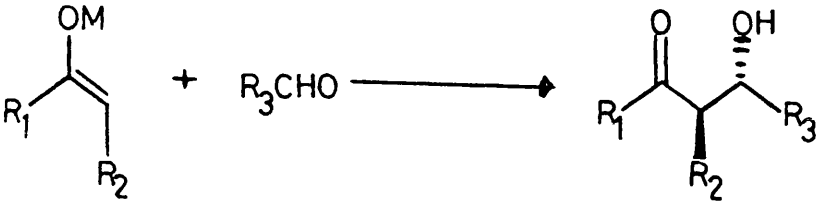
(a) Simple diastereoselectivity improves with an increase in the steric bulk of substituents R_1 on the enolate and R_3 on the aldehyde (Schemes 3 and 4 respectively).

(b) Z-enolates are usually more stereoselective than E-enolates (Scheme 5).



Z-enolate

syn aldol

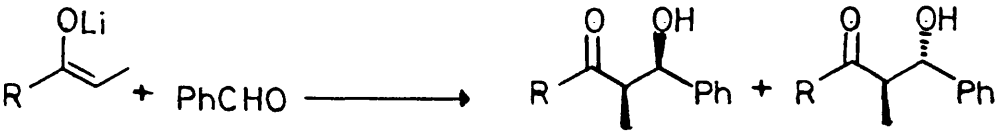


E-enolate

anti aldol

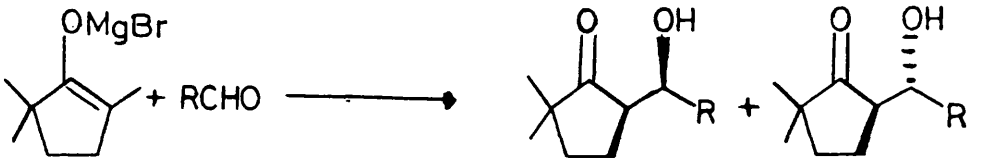
[M = Li, Na, K, Cs, MgX, AlX_2 and BR_2.]

Scheme 2



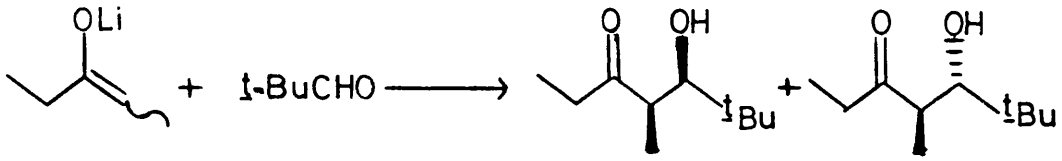
R	*syn*:*anti*
Ph	88:12
t-Bu	98: 2

Scheme 3[2]



R	*syn*:*anti*
Et	6:94
t-Bu	1:99

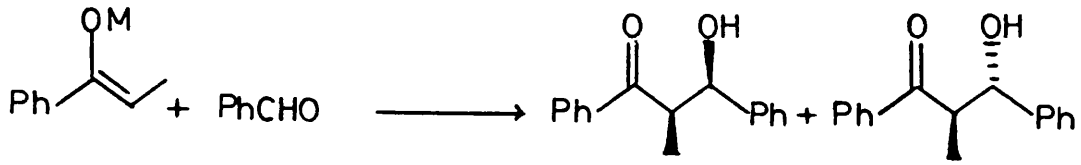
Scheme 4[5]



	syn:*anti*
Z-enolate	88:12
E-enolate	48:52

Scheme 5[6]

(c) Within Groups I → III metal enolates, the nature of the metal counterion, M, affects the selectivity. Boron enolates show better selectivity than other Groups I → III metal enolates (Scheme 6).



M	*syn*: *anti*
Li	88:12
B(*n*-Bu)$_2$	97: 3

Scheme 6[7]

The relationship between enolate geometry and simple diastereoselectivity of Groups I → III metal enolates has been explained in terms of 'closed or chelated' transition state models of the type first proposed by Zimmerman and Traxler in 1957.[8]

1.2.2 Closed transition state model

In the 'closed' transition state, it is assumed that the new carbon-carbon bond is partially formed and the negative charge is shared between two oxygen atoms. It is reasonable to assume, in such a transition state, that both oxygen atoms will be orientated towards the metal atom.

For Z-enolates, the transition states leading to the *syn* and *anti* aldols are shown in Figure 1. The dominant interaction is between R_1 and R_3 leading to a preference for (a) over (b), giving *syn* selectivity. As the size of R_1 and R_3 increases, the 1,3 diaxial interactions become stronger and stereoselectivity improves.

A similar pair of transition states is possible for the E-enolates (see Figure 2), the R_1-R_3 interaction now favouring the *anti* aldol.

The chair transition states depicted in Figures 1 and 2 can be modified to explain the observation that Z-enolates are more stereoselective than E-enolates when R_1 is small (Scheme 5).

It has been proposed that the difference in inherent stereoselectivity of Z- and E-enolates is due to skewing, or distortion of the transition states from the idealised staggered arrangement.[2,5] Skewing causes the carbonyl and enolate double bonds to move to *ca.* 90° to each other (Figure 3). In this situation, non-bonded interaction R_2-R_3 must be considered in addition to interaction R_1-R_3. The latter interaction is important for Z- and E-enolates and promotes transition state (a) and (c) respectively. The former interaction is more important for E-enolates than Z-enolates and leads to reaction *via* transition states (c) and (d). Hence the E-enolates are less selective when R_1 is small.

An alternative interpretation of the closed transition state model has been proposed by Evans and co-workers.[4a] In addition to the four symmetrical chair transition states depicted in Figures 1 and 2, the four boat transition states shown in Figure 4 were also considered. Simple stereoselectivity is now explained by assuming that a Z- or E-enolate can choose one

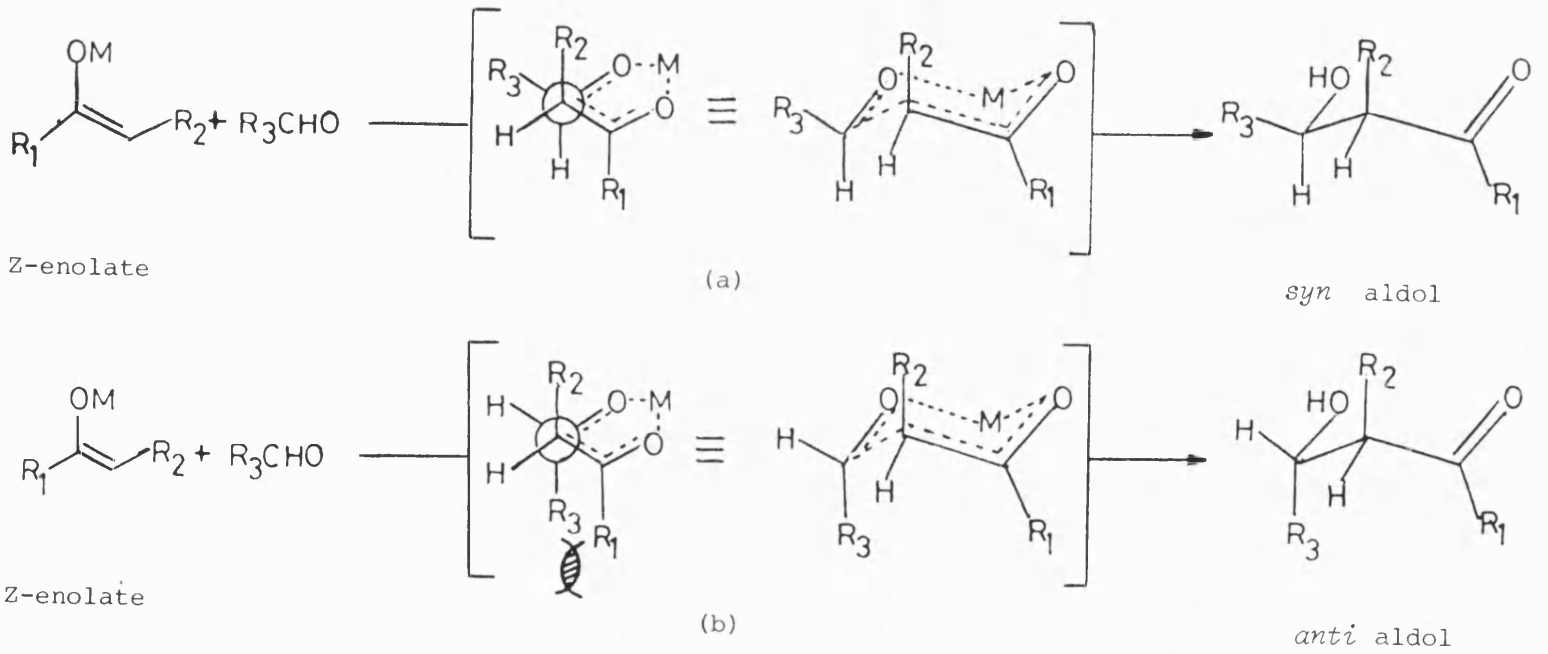


Figure 1 Symmetrical chair forms of closed transition state for Z-enolates

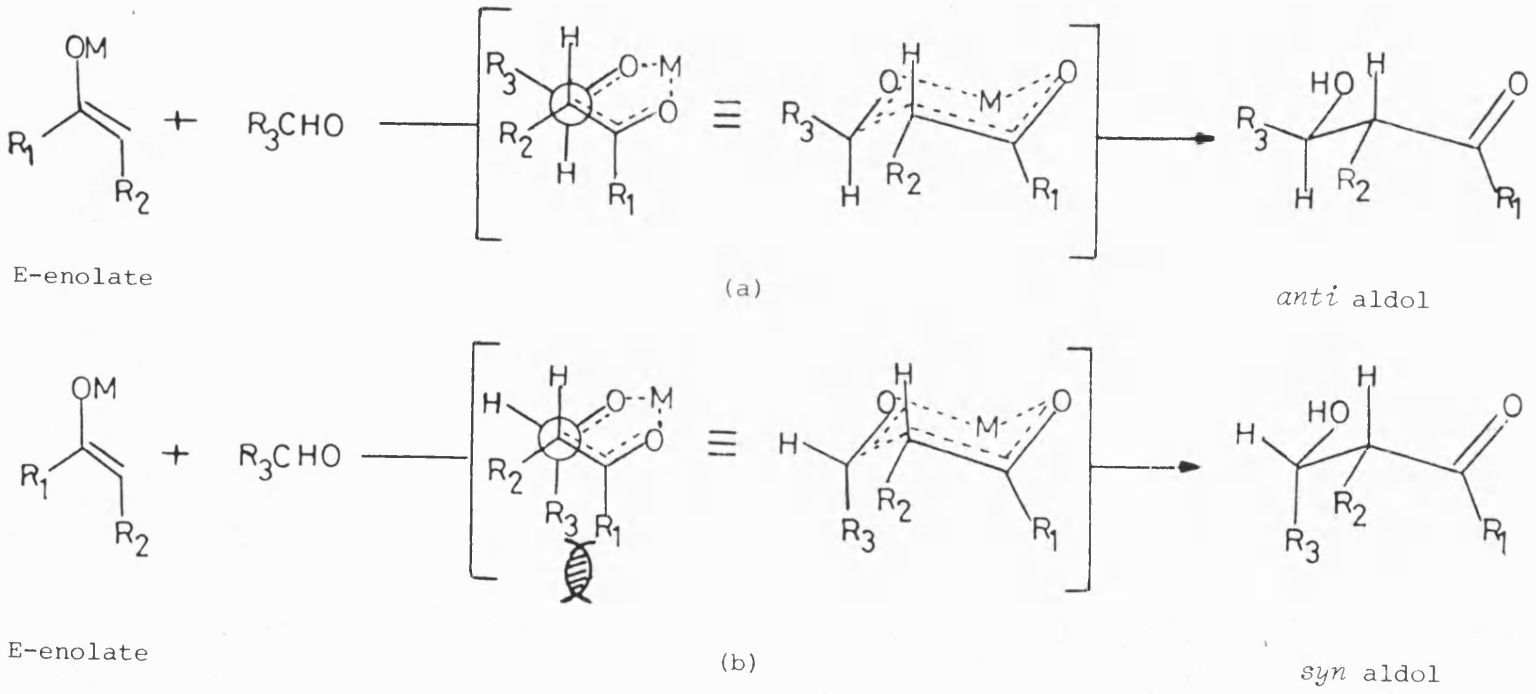
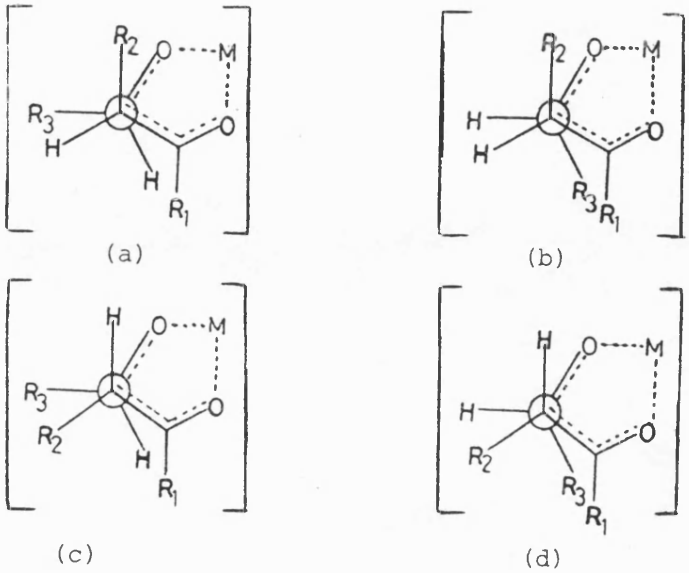


Figure 2 Symmetrical chair forms of closed transition state for E-enolates



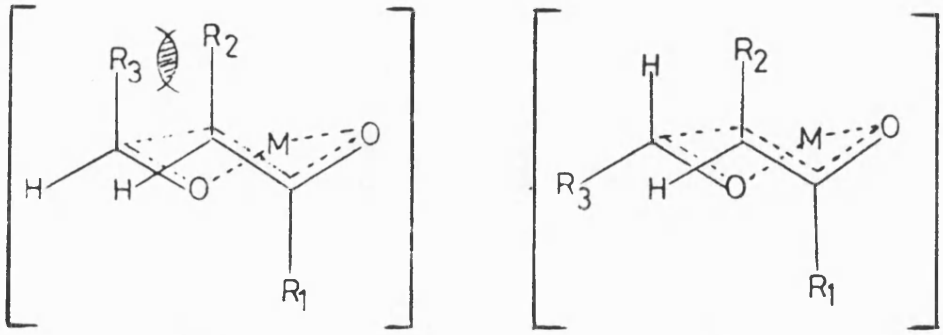
(a) Z-enolate → *syn* aldol (b) Z-enolate → *anti* aldol

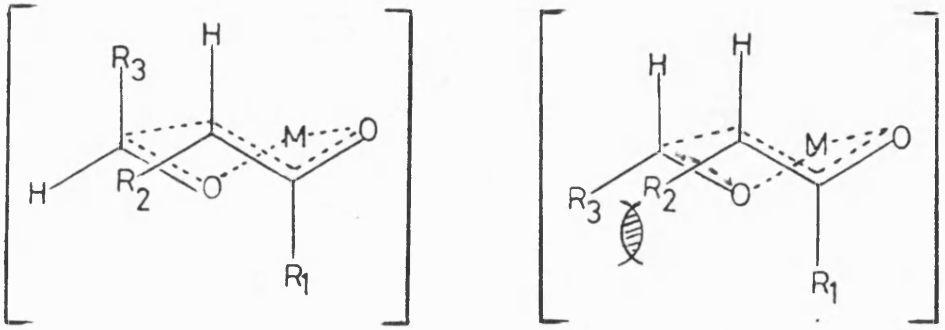
(c) E-enolate → *anti* aldol (d) E-enolate → *syn* aldol

Figure 3 Unsymmetrical chair forms of closed transition state

of the two chair transition states, or one of the two boat transition states. Of the boat transition states shown in Figure 4, (a) and (d) are considered unimportant because of R_2-R_3 eclipsing interactions. However, when the gauche R_2-R_3 interaction becomes important (large R_2), a Z-enolate may find chair transition state (a), as shown in Figure 1, less attractive than the boat transition state (b) shown in Figure 4.

The closed transition state model also explains why boron enolates are more stereoselective than other Groups I → III metal enolates[4b] (Scheme 5). Examination of average metal-oxygen bond lengths (Table 1), shows the B-O bond length is considerably shorter than the M-O bond length of other Groups I → III metals commonly used in aldol reactions. The closed transition state involving a boron enolate is consequently much tighter than transition states of enolates involving other metals, and steric effects are magnified.





(a) Z-enolate → *syn* aldol (b) Z-enolate → *anti* aldol

(c) E-enolate → *anti* aldol (d) E-enolate → *syn* aldol

Figure 4 Boat forms of closed transition state

Table 1

Average M-O bond lengths in Groups I → III metals

M	Average M-O bond length (Å)
Li	1.92-2.00
Mg	2.01-2.13
Al	1.92
B	1.36-1.47

It should be borne in mind that all the transition states so far discussed may be over-simplifications, since it is likely that lithium and other Groups I → III metal enolates exist and react as aggregates in ethereal solutions.[9] Nevertheless, they provide useful working hypotheses both to challenge and upon which to attempt predictions.

1.2.3 Enolsilanes (silyl enol ethers)

Although there has been a multitude of work on the stereochemistry of the aldol reaction between preformed Groups I → III metal enolates and aldehydes, much less is known about simple diastereoselection in the related reaction of enolsilanes with aldehydes. These reactions may be mediated by Lewis acids[10] or fluoride ion.[11]

Several examples of the Lewis acid-mediated aldol reaction of enolsilanes are shown in Scheme 7. Generally, variable levels of stereoselectivity have been observed.

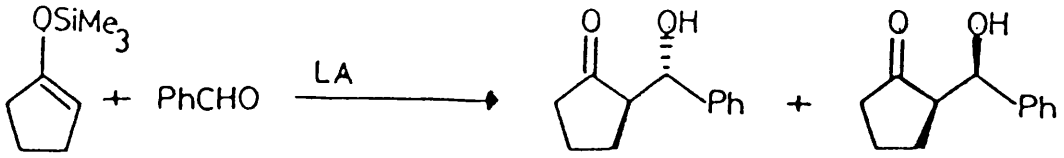
Fluoride mediated aldol reactions of enolsilanes and aldehyde have been studied by groups led by Noyori[12] and Heathcock.[13] The *syn* stereoisomer is usually the kinetic product, but the reactions are freely reversible and under thermodynamic conditions the *anti* diastereoisomer often predominates (see Scheme 8 and Table 2).

Table 2

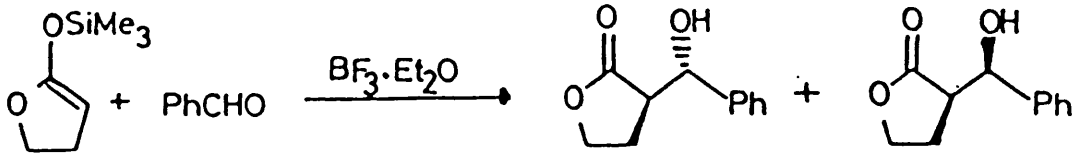
Time (min)	*syn*:*anti* (diastereoisomer ratio %)
15	88:12
30	86:14
60	79:21
120	50:50
180	19:81
960	5:95

A closely related aldol reaction is the tris(diethylamino)-sulphonium (TAS^+) difluorotrimethylsiliconate (3)-catalysed reaction of enolsilanes.[12,14] *syn*-Diastereoselectivity is usually observed regardless of the enolate stereochemistry. An example of such an aldol reaction is shown in Scheme 9.[14]

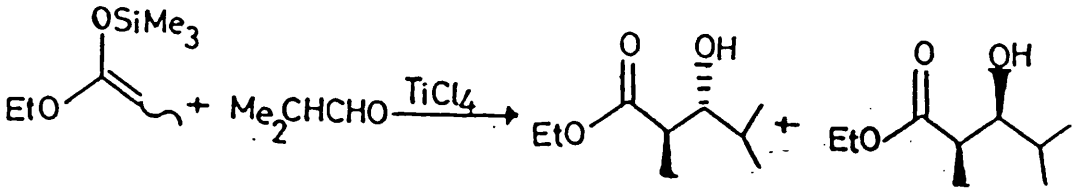
It is unclear whether aldol reactions mediated by (3) are proceeding under thermodynamic or kinetic control, but when the



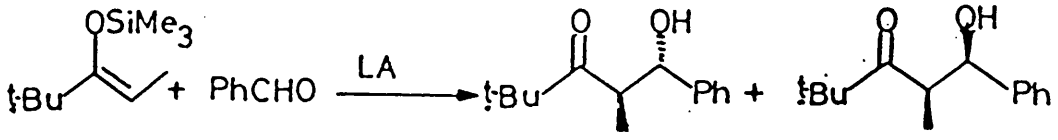
LA	*anti*:*syn*	Yield (%)	Ref
$BF_3.Et_2O$	60:40	78	10a
$TiCl_4$	50:50	68	10b



anti:*syn*	Yield (%)	Ref
39:61	82	10a



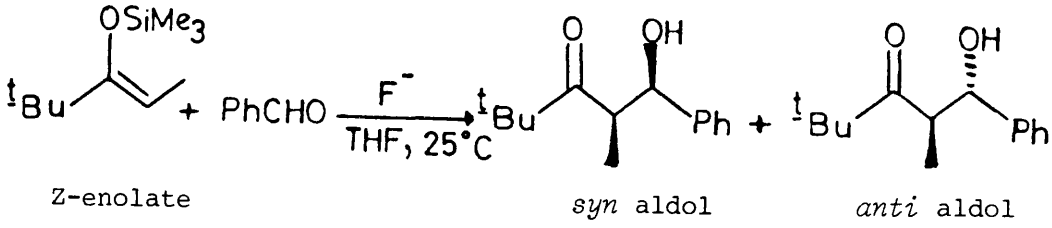
	anti:*syn*	Yield (%)	Ref
Z-enolate	52:48	77	10c
E-enolate	92:8	75	10c



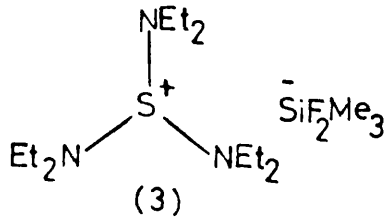
LA	*anti*:*syn*	Yield (%)	Ref
$TiCl_4$	95:5	93	10a
$BF_3.Et_2O$	95:5	95	10a
$SnCl_4$	95:5	72	10a

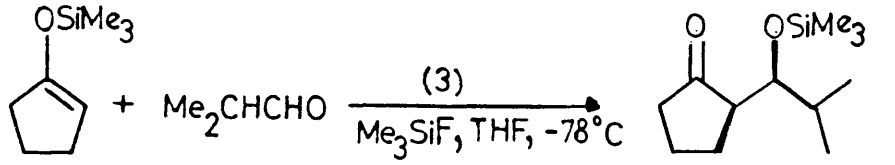
All reactions performed in DCM at -78 °C.

Scheme 7[10a-c]



Scheme 8[13]



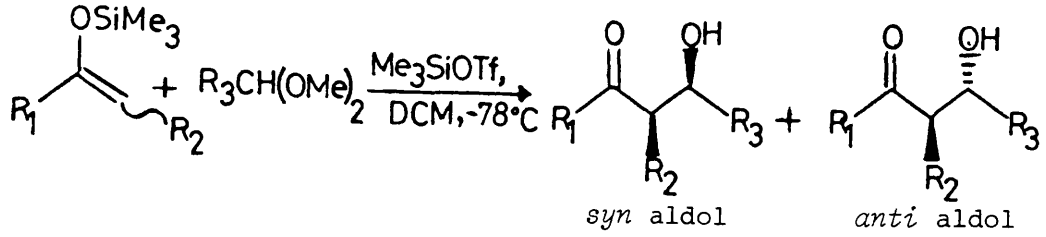


>99% *syn* isomer

Scheme 9[14]

reactions were performed at higher temperatures, a lower *syn*:*anti* diastereoisomer ratio was observed.[14]

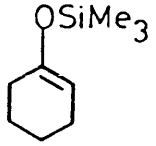
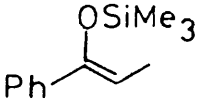
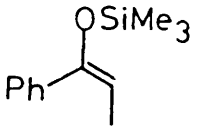
Another aldol addition reaction which shows enolate-structure-independent stereoselectivity is the trimethyltriflate-mediated aldol reaction of enolsilanes[15] with acetals (Scheme 10 and Table 3).



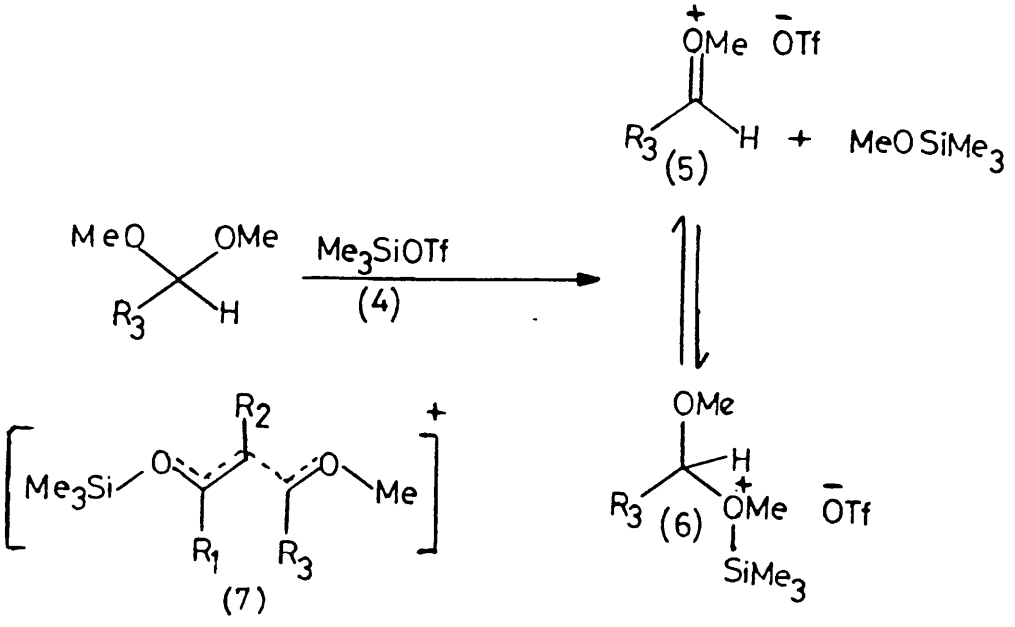
Scheme 10

Table 3

Trimethylsilyl triflate-catalysed aldol reaction of enolsilanes with acetals

Enol silane	Acetal	*syn*:*anti*	Yield (%)
	$PhCH(OMe)_2$	93: 7	89
	$Me_2CHCH(OMe)_2$	86:14	95
	$PhCH(OMe)_2$	84:16	97
	$PhCH(OMe)_2$	71:29	83

It is believed that trimethylsilyl triflate (4) is able to activate the acetal by forming the intermediate electrophilic species (5) and (6).[15] These putative electrophiles then undergo reactions with enolsilanes *via* the extended transition state (7), in Scheme 11.



Scheme 11

1.2.4 Transition state models used to explain diastereoselectivity observed in aldol reactions involving enolsilanes

The open or acyclic transition state first proposed by Noyori[14,16] and later modified by Heathcock[10a] has been used to explain the variable levels of stereoselectivity observed in Lewis acid-mediated aldol reactions of enolsilanes with achiral aldehydes.

The staggered conformations for Z-enolsilanes and E-enolsilanes for an open transition state are depicted in Figures 5 and 6 respectively. It is assumed the Lewis acid occupies a co-ordination site on the carbonyl oxygen such that it is *cis* to the aldehyde hydrogen atom.

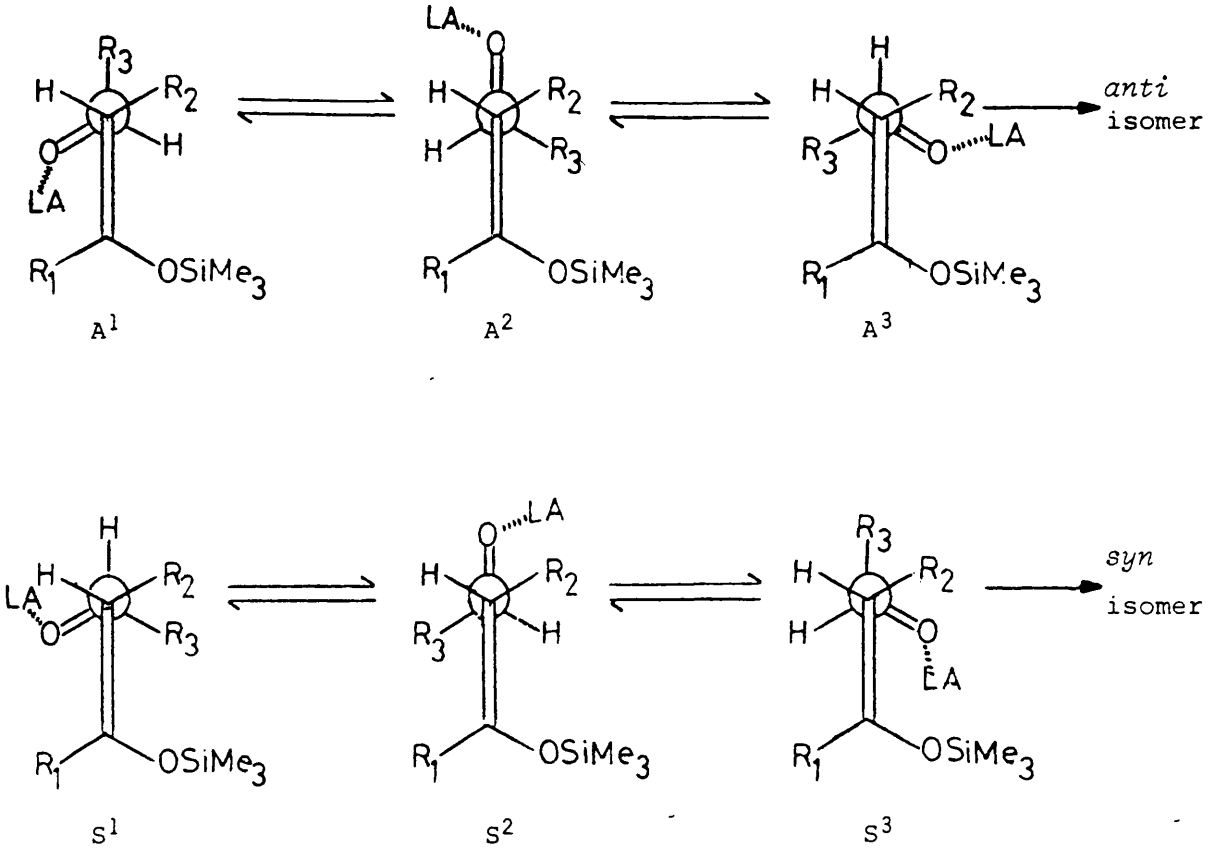


Figure 5 Open transition state model for Z-enolsilanes

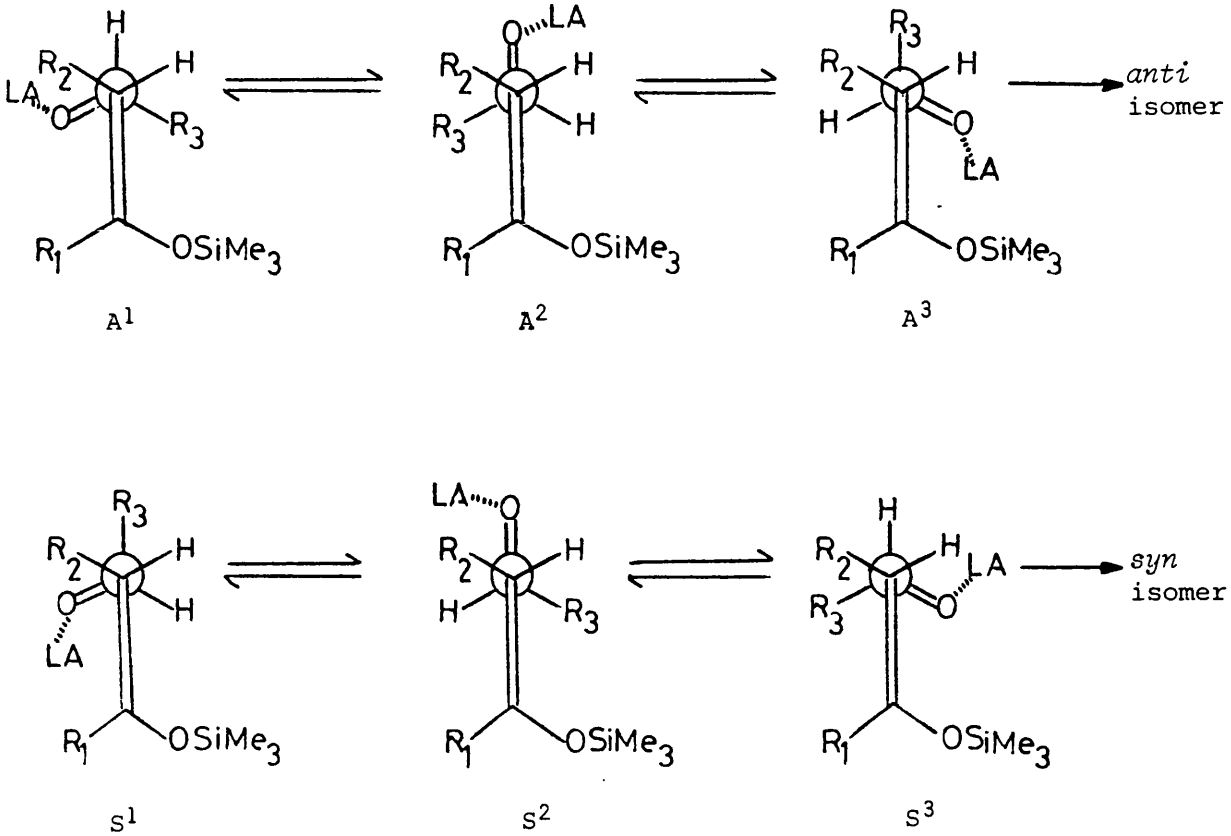


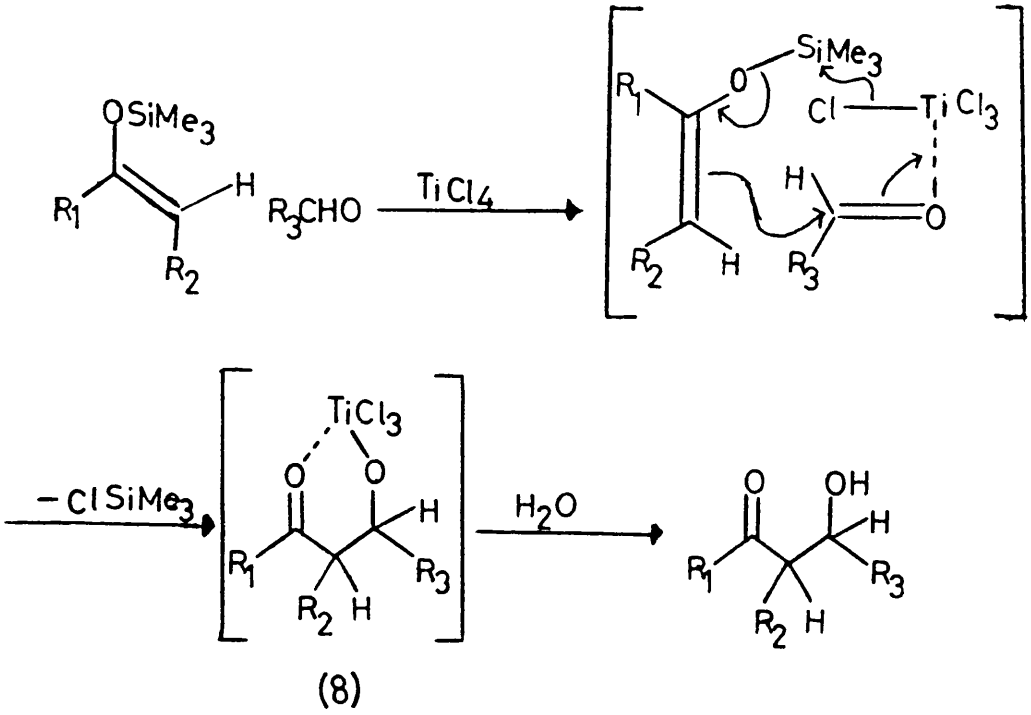
Figure 6 Open transition state model for E-enolsilanes

For a geometrically pure enolsilane, the stereoselectivity of the reaction depends upon the relative proportions of each transition state conformer. Conformers A^3 and S^3 may be neglected for both Z- and E-enolsilanes because of unfavourable dipole-dipole interactions of the two carbon-oxygen bonds. The population of conformers A^1, A^2, S^1 and S^2 depend upon the magnitude of the non-bonded interaction R_3-R_2 and to a lesser extent on non-bonded interactions R_3-R_1, R_3-O-silyl and LA-O-silyl. For enolsilanes in which R_1 and R_2 are both small, there is little energy difference between transition state conformers A^1, A^2, S^1 and S^2 and poor stereoselectivity is observed.

An alternative transition state model which has been used to explain diastereoselectivity of $TiCl_4$ mediated aldol reactions of enolsilanes is the cyclic or chelated model proposed by

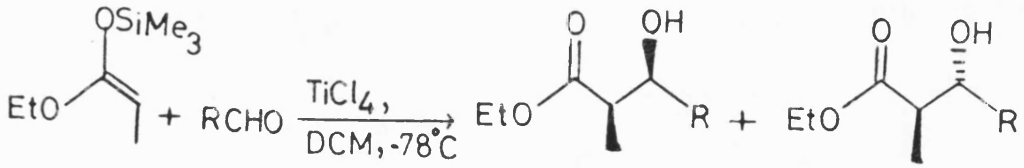
Mukaiyama and co-workers.[10b] (Scheme 12). This model takes account of the high affinity $TiCl_4$ has for oxygen and suggests the formation of an intermediate titanium-chelated transition state (8).

Compare the transition state with analogous lithium-chelated transition states discussed earlier (section 1.2.2).



Scheme 12

Chan and co-workers[10c] used a similar chelated transition state to explain the high levels of *anti* selectivity observed in the $TiCl_4$-mediated aldol reaction of the E-enolsilane derived from ethyl propionate (Scheme 13). The favoured chair-like titanium(IV) chelate, in which the R_3 group is equatorial, leads to the *anti* diastereoisomer (Figure 7).



R	*syn*:*anti*	Yield (%)
i-Pr	<2:98	75
$Me(CH_2)_4$	6:94	77
Ph	25:75	79

Scheme 13

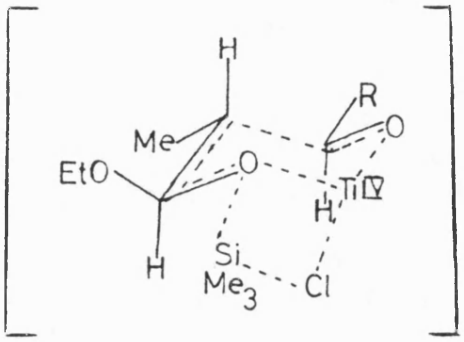
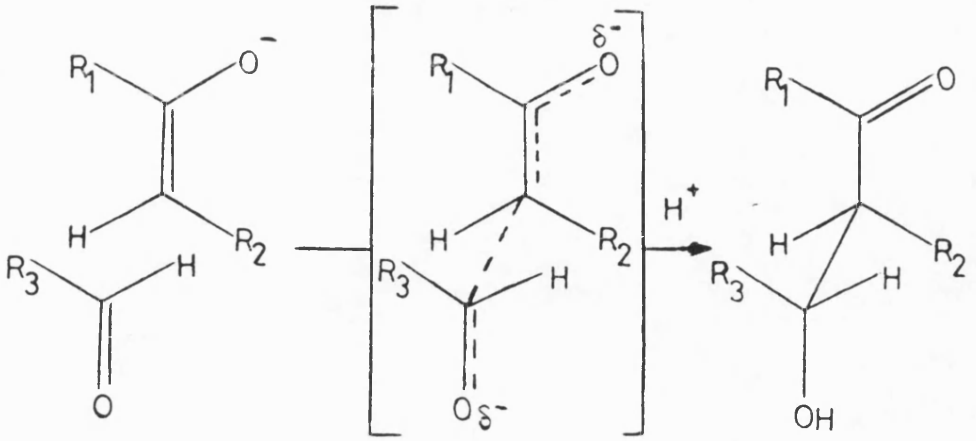


Figure 7

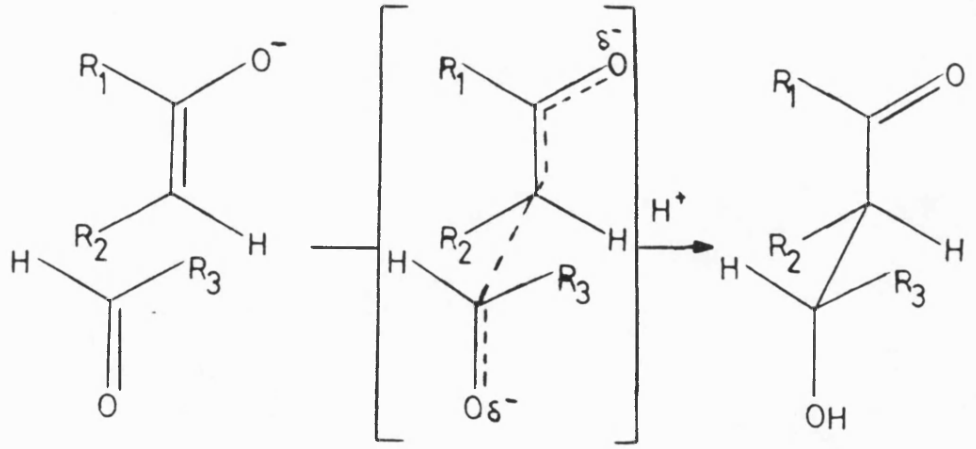
Fluoride- and $TAS^+Me_3SiF_2^-$ (3)-catalysed aldol reaction of enolsilanes are believed to react *via* open transition states.[12] In both these reactions naked enolates (negligible bonding between the anion and cation) are generated and there is a build-up of negative charge in the transition state. The oxygen atoms orientate themselves as far apart as possible. The diastereoselectivity of the reaction is determined by the magnitude of non-bonded interaction R_3-R_2. Under kinetic conditions, both Z- and E-enolsilanes give mainly *syn* diastereoisomers (Figures 8 and 9 respectively).

A similar open transition state hypothesis has been used by Noyori and co-workers[15] to explain the *syn* selectivity observed in TMSOTf (4)-mediated aldol reactions of enolsilanes with acetals.



Z-enolate *syn*-diastereoisomer

Figure 8 Open transition state model for 'naked' Z-enolate

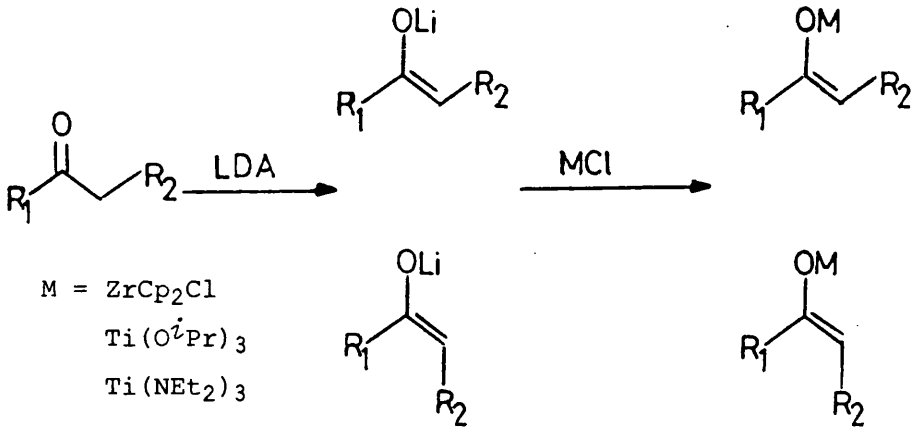


E-enolate *syn*-diastereoisomer

Figure 9 Open transition state model for 'naked' E-enolate

1.2.5 Other metal enolates

Aldol reactions involving zirconium[17] and titanium[18] enolates have been investigated by several groups. Both types of metal enolates were prepared by metal exchange reactions from corresponding lithium enolates. The geometry of the enolate is retained during the transmetallation reaction[17a] (Scheme 14).

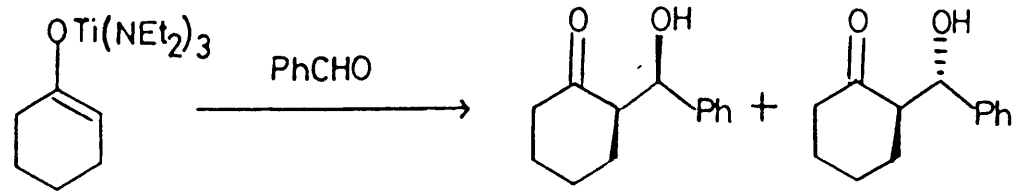


Scheme 14

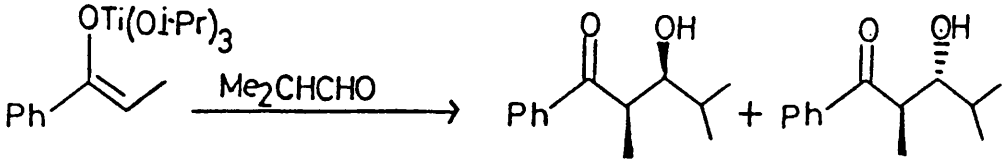
In general, zirconium and titanium enolates show good *syn* diastereoselectivity, irrespective of the enolate geometry. The use of titanium enolates particularly favours *syn* aldol formation from cyclic ketones (Scheme 15).

The reason for the inherent *syn* selectivity of these enolates is uncertain, although it has been suggested that the O-Zr-O and O-Ti-O bond lengths and bond angles are of appropriate length and size to allow distortion from usual pericyclic chair and boat transition states and this may explain the diastereoselectivity,[17a] the E-enolate reacting *via* a pseudo-boat transition state and the Z-enolate reacting *via* a pseudo-chair transition state. Yamamoto and co-workers[17b] have suggested that the zirconium enolates may be reacting *via* an open transition state. However, the observation that bis(pentamethylcyclopentadienyl)-zirconium enolates do not undergo aldol reactions suggest that ligation of the aldehyde is an obligatory step in the reaction.[4b]

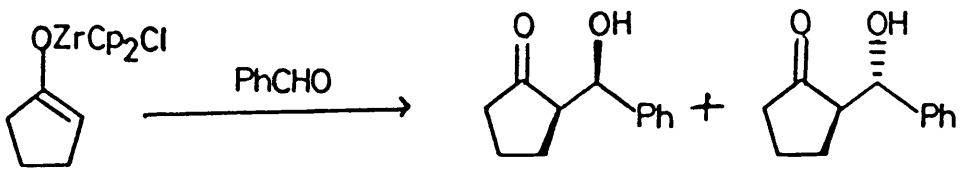
The nature of the ligands attached to the metal enolate can also influence the selectivity. Procter and co-workers[19] have recently shown that when the titanium enolate was substituted



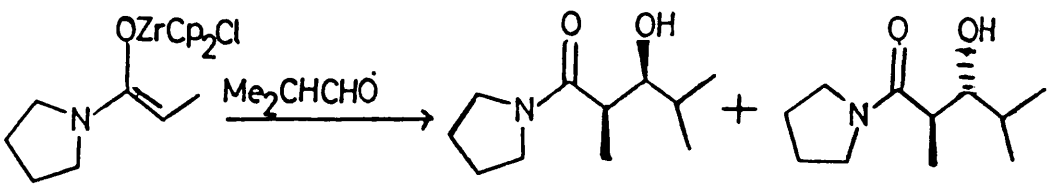
syn:*anti*	Yield (%)	Ref
97:3	*ca.* 70	18a



syn:*anti*	Yield (%)	Ref
95:5	*ca.* 70	18a



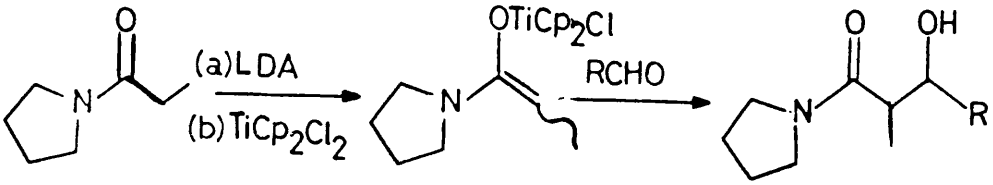
syn:*anti*	Yield (%)	Ref
74:26	82	17b



syn:*anti*	Yield (%)	Ref
95:5	80	17a

Scheme 15

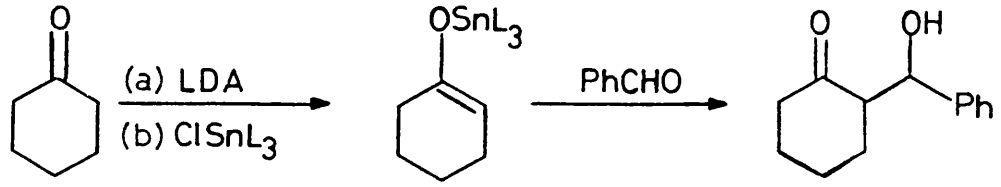
with bulky cyclopentadienyl ligands, the expected *syn* stereoselectivity was reversed and the *anti* isomer predominated (Scheme 16). No explanation for the reversal of simple diastereoselectivity was given.



	R	*syn*:*anti*	Yield (%)
Enolate stereochemistry not known	Et	21:79	65
	i-Pr	13:87	64
	Ph	2:98	68

Scheme 16

Similar ligand effects have been observed with other metal enolates. Yamamoto[20] and Stille[21] have independently investigated the kinetic aldol reaction between the tin(IV) enolate derived from cyclohexanone and benzaldehyde (Scheme 17).



L_3	*syn*:*anti*	Yield (%)	Ref
Ph	71:29	80	20
n-Bu	20:80	78	21

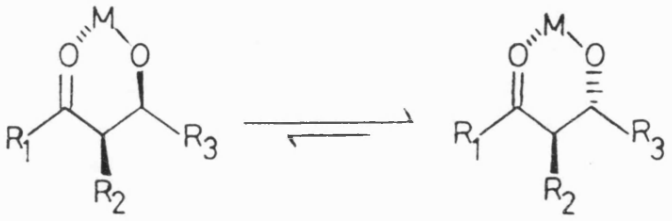
Scheme 17

When the tin(IV) metal was substituted with a bulky phenyl ligand, modest *syn* selectivity was observed. However, when substituted with smaller alkyl groups, the *anti* diastereoisomer predominated.

Although several methods are now available to achieve good *syn* simple stereoselectivity from both Z- and E-enolates under conditions of kinetic control, it is more difficult to achieve similar levels of *anti* stereoselectivity. One method by which it has been possible to exercise modest *anti* stereoselectivity is to perform the aldol reaction under equilibrating conditions.

1.3 Simple Diastereoselectivity under Thermodynamic Control

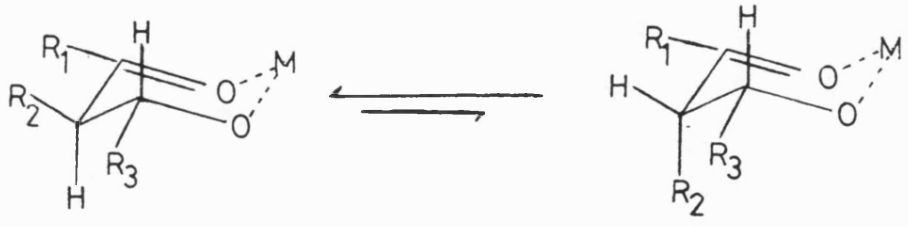
The aldol reaction is easily reversible and *syn/anti* equilibration is often observed when an ethereal solution of the aldolate (salt of aldol) is allowed to stand for a period of time (Scheme 18).



syn aldolate *anti* aldolate

Scheme 18

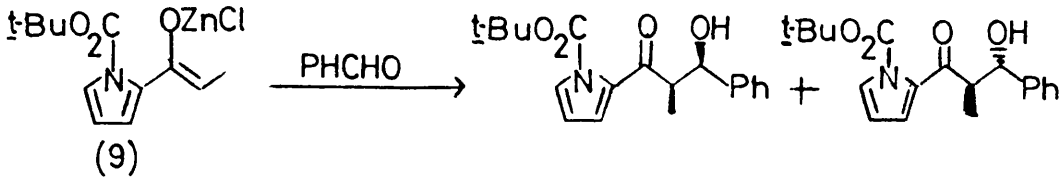
Under equilibration conditions the *anti* isomers of the aldolates are usually more stable than the *syn* isomers, since their chair-like conformations have the maximum number of equatorial substituents (Figure 10).



anti aldolate *syn* aldolate

Figure 10

Equilibrations have been used to achieve *anti* stereoselection. House and co-workers[22] showed that the counterions of Zn^{2+} and Mg^{2+} were able to enhance the thermodynamic *anti* diastereoselectivity in many cases. The aldol reaction of the Z-enolate (9) under both kinetic (-78 °C) and equilibrating conditions provide an example of this technique,[4a] (Scheme 19).



(9)

Temperature °C	*syn*:*anti*
-78	75:25
+ 4	25:75

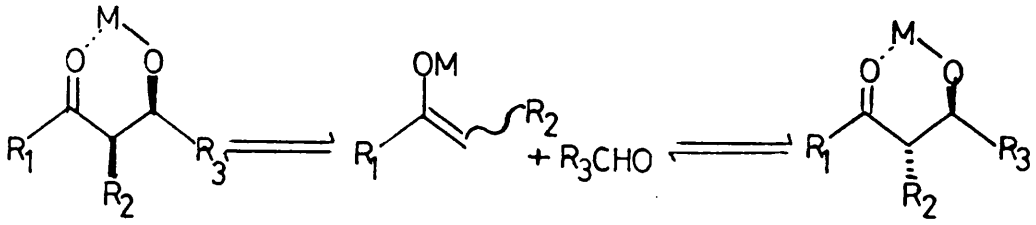
Scheme 19

1.3.1 Mechanism of *syn/anti* interconversion and factors which control the rate of equilibration

Two mechanisms have been advanced to explain the interconversion of *syn/anti* aldolates. The most widely quoted is the reverse-aldol process[4b] (Scheme 20). Another possible mechanism is *via* a base catalysed enolisation process (Scheme 21). Intermediates such as (10) are well documented as useful synthetic intermediates.[23]

The rate of *syn/anti* equilibration depends upon a number of factors, some of which are as follows:-

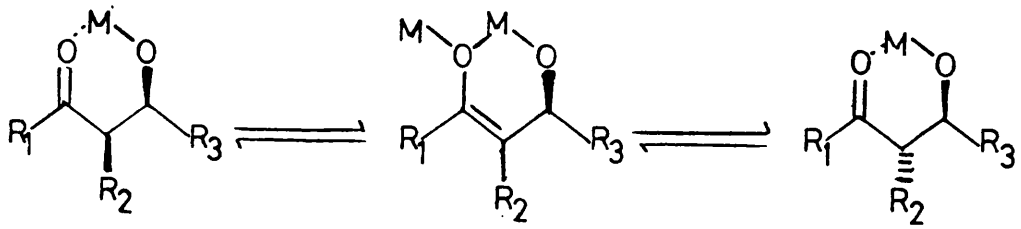
(i) The nature of the counterion, M. In general, counterions that are strongly chelated by the two oxygens of the aldolate (B, Al, Li) stabilise



syn aldolate

anti aldolate

Scheme 20



(10)

syn aldolate

anti aldolate

Scheme 21

it and retard the reverse-aldol process. Aldolates are more likely to undergo *syn/anti* equilibration when the counterion is one that is largely dissociated (K, Na, $R_4N)^+$.

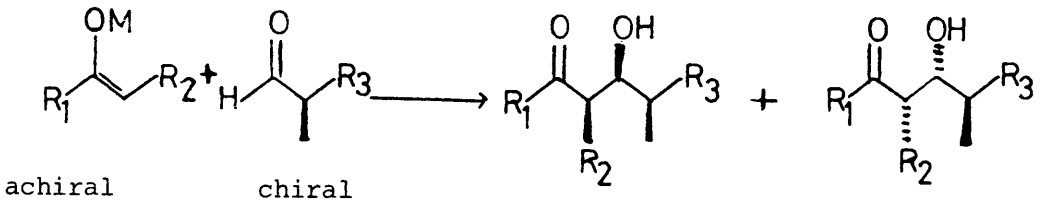
(ii) Steric crowding in an aldolate encourages *syn/anti* equilibration. The reverse-aldol mechanism is more likely when there is steric repulsion between substituents R_2 and R_3 of the aldolate.

(iii) Equilibration is promoted by structural modifications that serve to make the enolate less basic. Thus, aldolates derived from ketone enolates are more likely to suffer reverse aldolisation than are aldolates derived from esters, amides or carboxylate salts. *syn/anti* Equilibrations are slow if the enolate which would result from a reverse-aldol process has a high inherent diastereoselectivity.

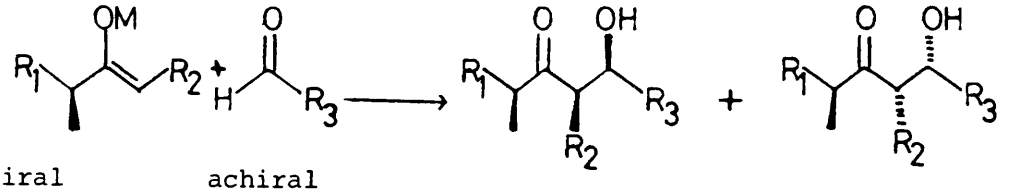
1.4 Diastereofacial Selectivity

The aldol reaction can show two distinct kinds of stereoselection. When two new asymmetric carbons are formed, they may have either the *syn* or *anti* relative configuration. This kind of stereoselection is termed simple diastereoselection and methods of controlling it have been discussed in the preceding section.

A different kind of stereoselection is possible when either reactant is chiral (Scheme 22). For example, addition of a Z-enolate to a chiral aldehyde can give two *syn* aldols, resulting from attack on either of the diastereotopic faces of the aldehyde. Similarly, if the enolate is chiral and the aldehyde is achiral, there are also two *syn* aldols resulting from attack at the diastereotopic faces of the enolate. This kind of stereoselection is termed diastereofacial selectivity[4b] and methods used to control it are discussed in the following section.



achiral Z-enolate chiral aldehyde



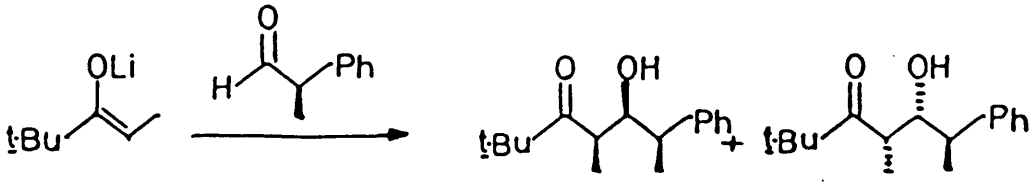
chiral Z-enolate achiral aldehyde

The enolates depicted above are assumed to have high inherent *syn* simple stereoselectivity.

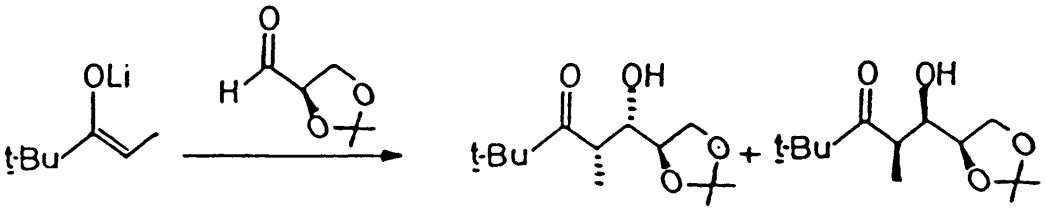
Scheme 22

1.4.1 Chiral aldehydes

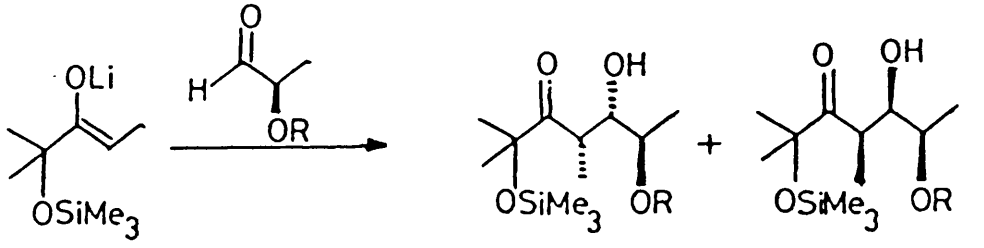
Examples of the type and level of diastereofacial selectivity normally observed in aldol reactions between chiral aldehydes and achiral enolates are shown in Scheme 23. The aldehydes normally show low to moderate diastereofacial selectivity (<6:1), with the stereochemistry of the major product being that predicted by the Felkin-Anh model for α-asymmetric induction.[24]



86:14 Ref 2



85:15 Ref 24

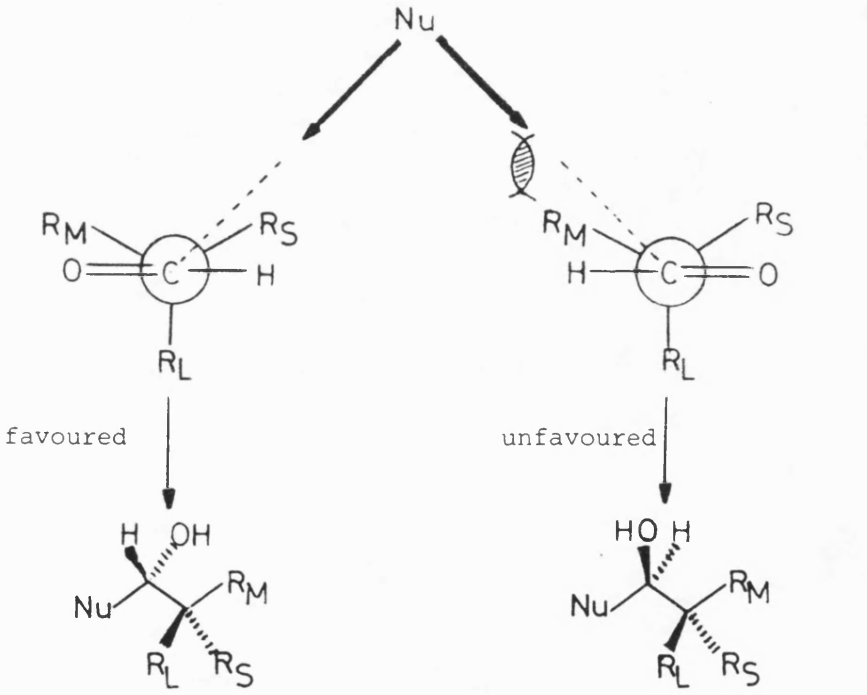


67:33 Ref 4c

R: CH_2OCH_2Ph

Scheme 23

For aldehydes containing an α-asymmetric carbon, the favoured conformation is one in which the largest α-substituent is perpendicular to the carbonyl bond. If the reactants are inclined at 110° to adopt the Burgi-Dunitz trajectory,[25] then the major stereoisomer will be that produced by the incoming nucleophile attacking at the least hindered site in the plane opposite the large α-substituent (Figure 11). In the case of α-alkoxy aldehydes it is assumed that the α-oxygen is the largest group (R_L) at the asymmetric centre.[24a]



Substituents at α-asymmetric carbon

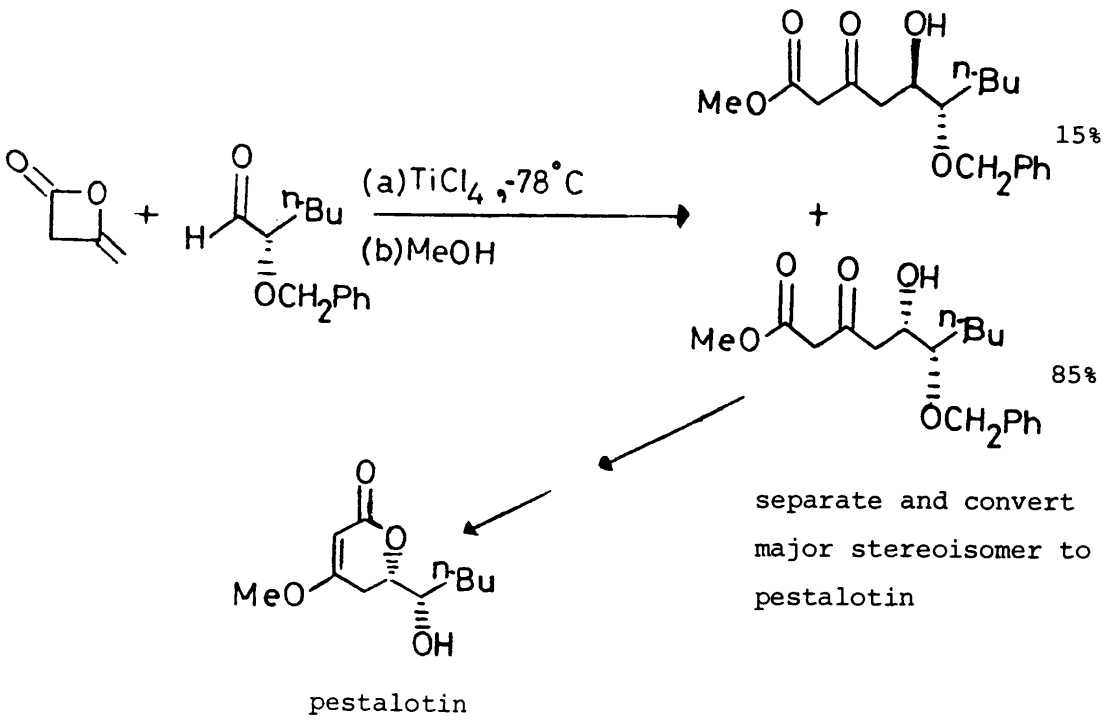
R_L = large

R_M = medium

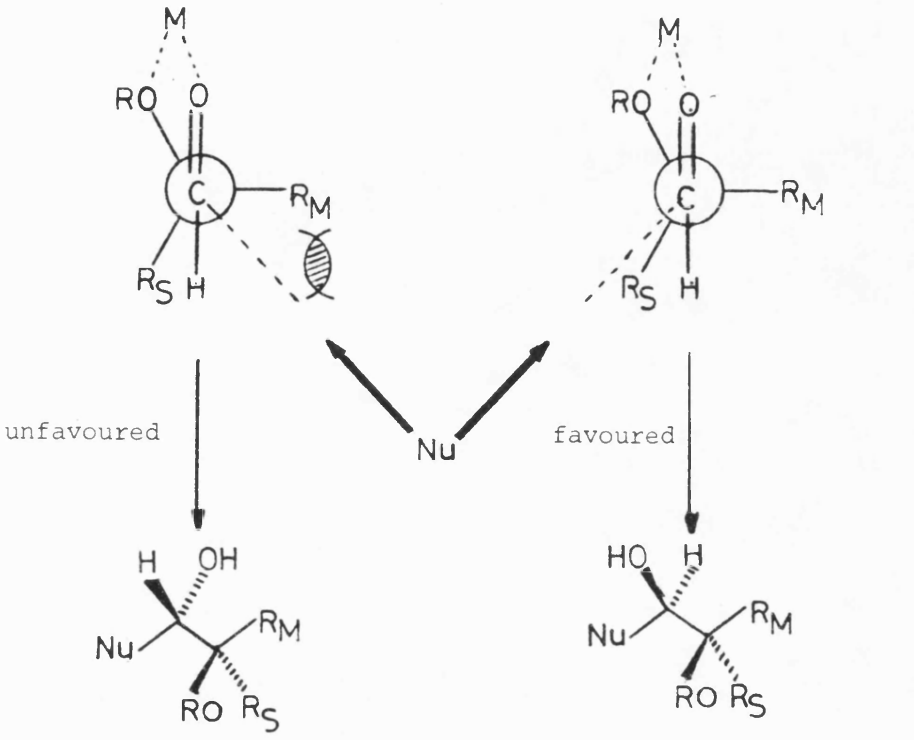
R_S = small

Figure 11

In a few cases, particularly when the metal counterion shows strong Lewis acid character, the major product from aldol reactions has a diastereofacial preference which is opposite to that predicted by the Felkin-Anh model for α-asymmetric induction. In these cases the diastereofacial selectivity is thought to be controlled by a chelated transition state.[26] An example of such a reaction was used in the synthesis of the natural product pestalotin[27] (Scheme 24), the stereoselectivity of the addition reaction being explained using the α-chelated transition state shown in Figure 12, where attack takes place faster from the less hindered face.



Scheme 24



Minor stereoisomer Major stereoisomer

Substituents at α-asymmetric centre

RO = large

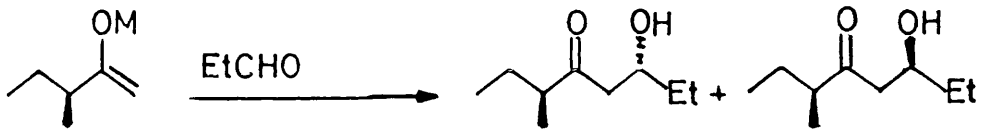
R_M = medium

R_S = small

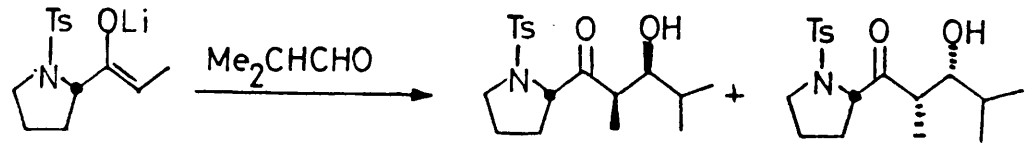
Figure 12

1.4.2 Chiral enolates

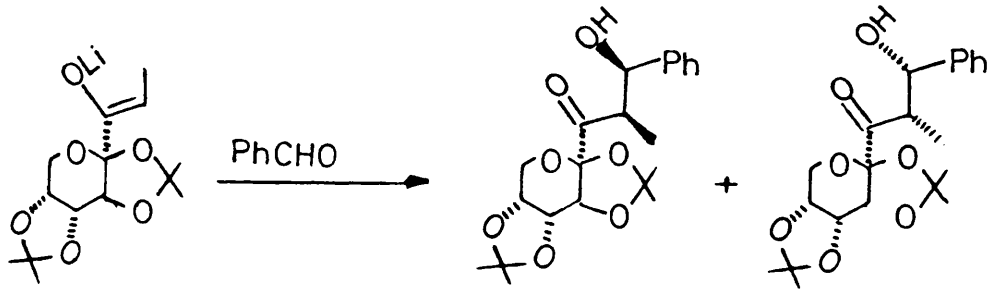
Aldol reactions between chiral enolates and achiral aldehydes generally show low to moderate levels of diastereofacial selectivity (Scheme 25). The diastereofacial selectivity is similar to, or slightly better than, that observed in reactions between chiral aldehydes and achiral enolates.



M			Ref
Li	57	43	28
B(*n*-Bu)$_2$	63	37	29



70:30 Ref 29



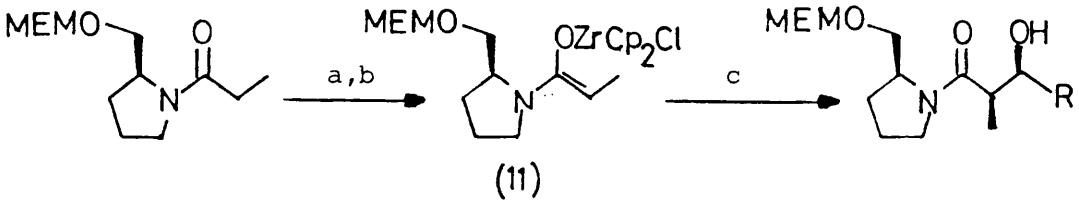
79:21 Ref 30

Scheme 25

1.4.3. Enantioselective chiral enolates

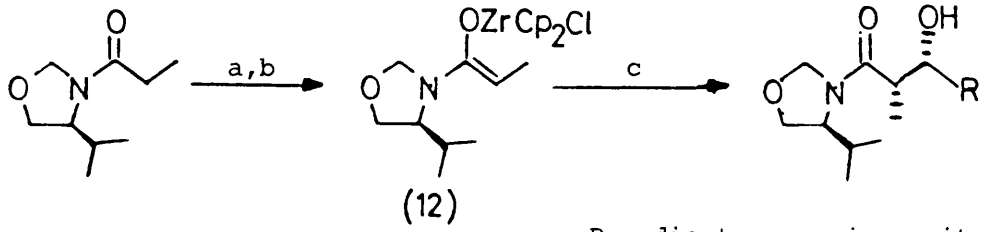
In the last ten years, several chiral enolate reagents have been developed which show exceptionally high inherent simple diastereoselectivity in aldol reactions. When the sense of chirality at the newly created asymmetric centre in the aldol is determined completely by the sense of chirality of the enolate, the enolates are said to be enantioselective.

One of the first classes of enantioselective reagents to be discovered were the zirconium enolates of chiral propionamides (11) and (12).[31] Enolates (11) and (12) show exceptionally high diastereoselectivity in aldol reactions with achiral aldehydes (Scheme 26).



(11)

R	diastereomeric purity (%)
i-Pr	>96
Ph	>96
n-Bu	>96



(12)

R	diastereomeric purity (%)
i-Pr	>98
Ph	97
n-Bu	95

MEM = methoxymethyl

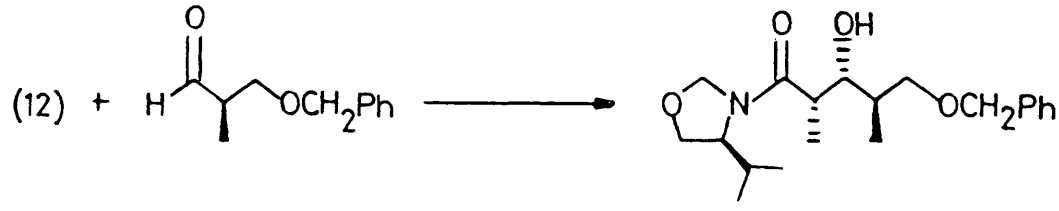
[a]LDA , THF, -78 °C; [b]$ZrCp_2Cl_2$, THF, -40 °C; [c]RCHO

Scheme 26[31]

The inherent diastereofacial preference (>80:1) of zirconium enolates (11) and (12) is much greater than the modest stereoselectivity of most chiral aldehydes (<6:1), so that in aldol reactions between chiral aldehydes and enolates (11) and (12), the stereochemistry of the product is determined almost completely by the inherent diastereofacial preference of the enolate. An example of this is shown in the aldol reaction between enolate (12) and the (S) and (R) enantiomers of 3-benzyloxy-2-methylpropanal (Scheme 27).[31] Enolate (12) reacts with the (R) enantiomer to give mainly a single diastereoisomer (95% diastereomeric purity), even though the innate diastereofacial preference of the aldehyde is opposite to that of the enolate.

(S) enantiomer

diastereomeric purity (%)
>99

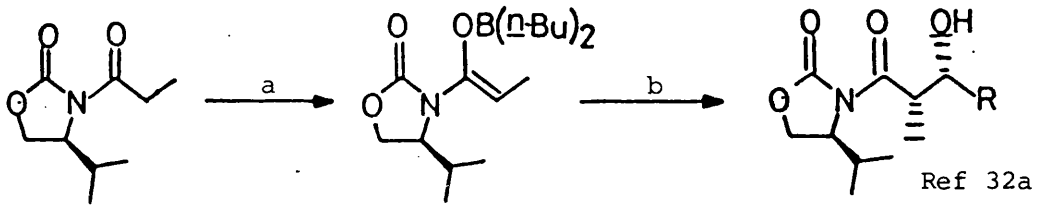


(R) enantiomer

diastereomeric purity (%)
>95

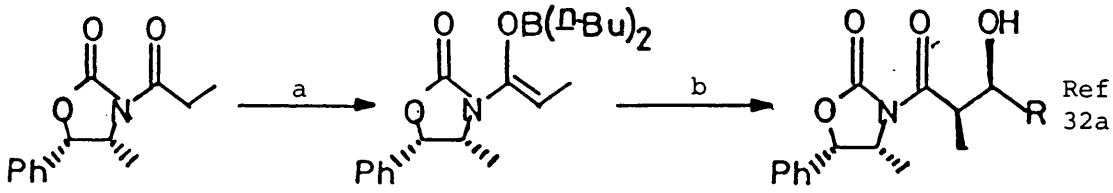
Scheme 27

A closely related and complementary class of enantioselective reagents is the boron enolates (13) and (14).[32] These enolates have a very high diastereofacial preference in aldol reactions (Scheme 28).



Ref 32a

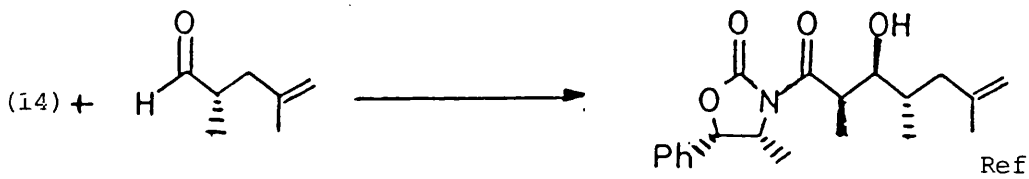
(13)	R	diastereomeric purity (%)
	i-Pr	99.8
	Ph	>99.8
	n-Bu	99.3



Ref 32a

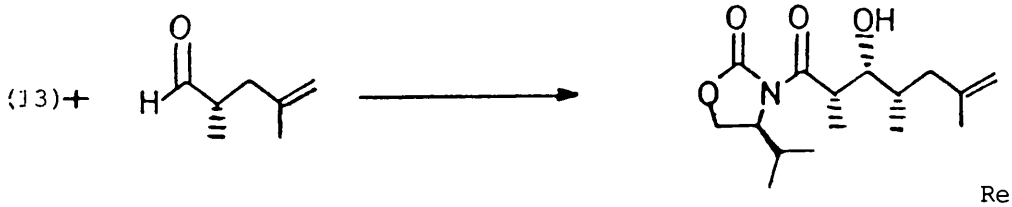
(14)	R	diastereomeric purity (%)
	i-Pr	>99.8
	Ph	>99.8
	n-Bu	>99.8

[a] $(n\text{-Bu})_2$BOTf, EtN-$(i\text{-Pr})_2$; [b] RCHO



Ref 32b

>99.8% diastereomeric purity (%)



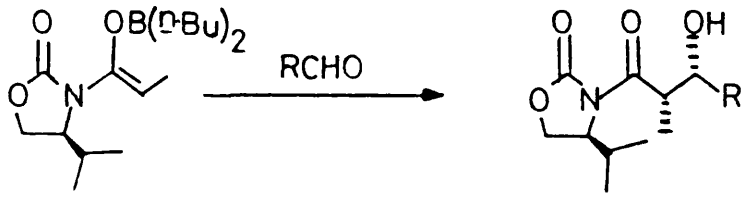
Ref 32b

>99.8% diastereomeric purity

Scheme 28 [32a,b]

A mechanistic rationale has been advanced by Evans[4a] to explain the kinetic stereoselectivity observed in the aldol reaction of the chiral enolate (13), (Figure 13).

The aldehyde only approaches the enolate from the side which faces away from the large isopropyl substituent on the oxazolidinone, so that of the four diastereomeric transition states A, B, C and D, only the two, (A and D), in which the isopropyl group is in the *exo* position, must be taken into consideration. Stereoselectivity is observed when one of them is clearly favoured. In the case of propionic enolate (13), the mutual repulsion of the isopropyl group and methyl substituent means transition state A is favoured, so that stereoselectivity is as shown in Scheme 29.



(13)

Scheme 29

Similar transition states have been suggested to explain the diastereofacial selectivity of zirconium enolates (11) and (12) and boron enolate (14).[4a]

Chiral amide and chiral imide enolates are very important tools for asymmetric aldol synthesis. The chiral inducing fragment can be conveniently removed and recycled. For the β-hydroxyamides resulting from aldol reactions of enolate (11), acid hydrolysis of the MEM group is accompanied by rapid N to O acyl transfer.

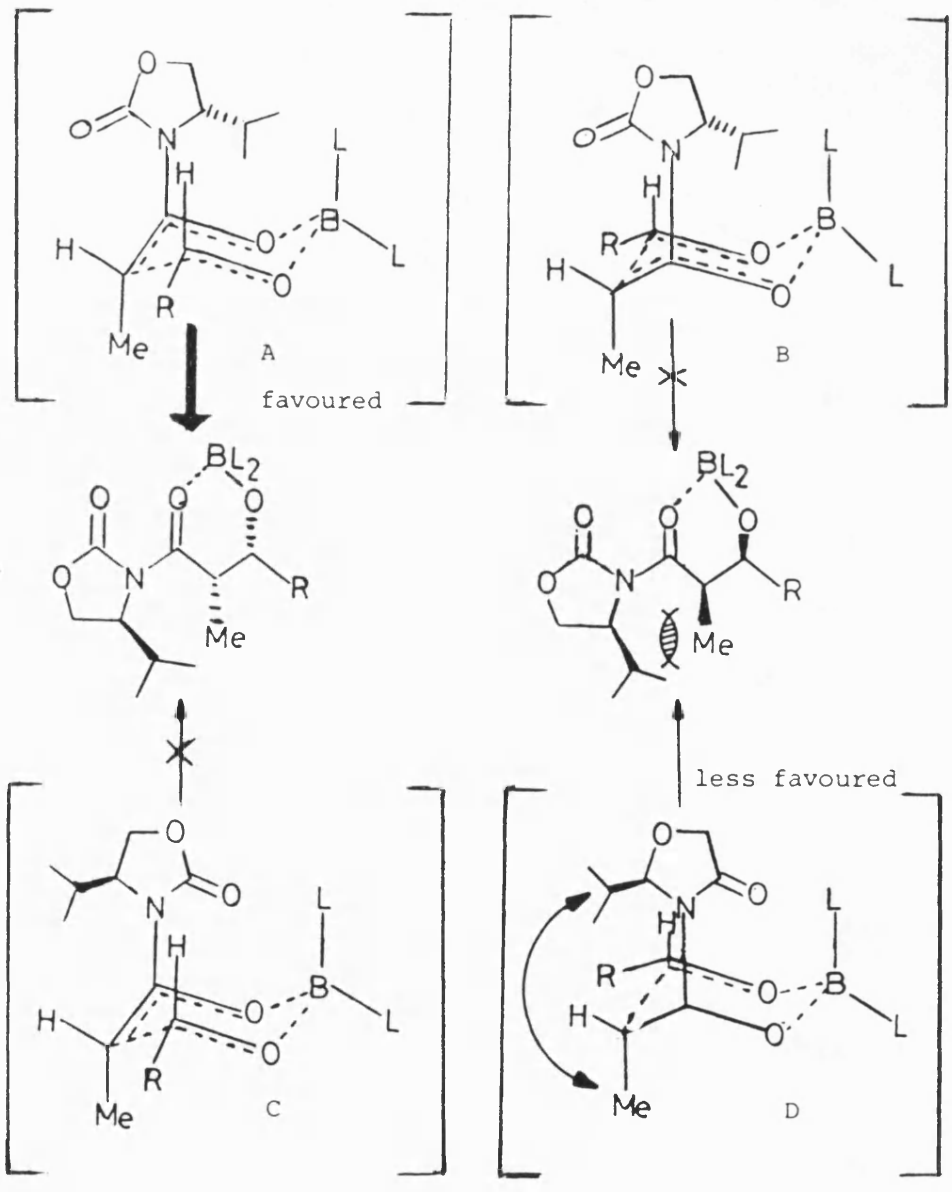
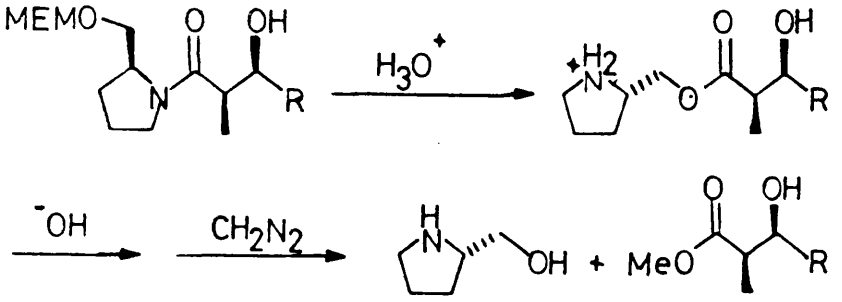
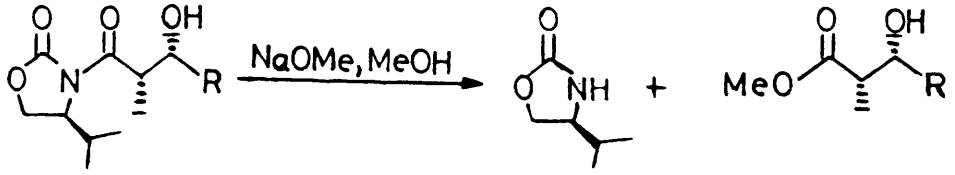


Figure 13

Basification of the resulting ammonium ester gives the chiral auxiliary and optically-active β-hydroxy acid,[31] (Scheme 30). In a similar manner, the β-hydroxyimides produced from enolates (13) and (14) can be hydrolysed to the corresponding β-hydroxy acids[4b] (Scheme 31).

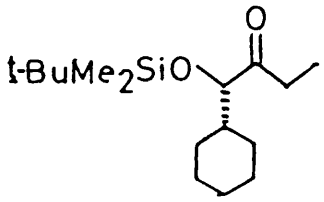


Scheme 30

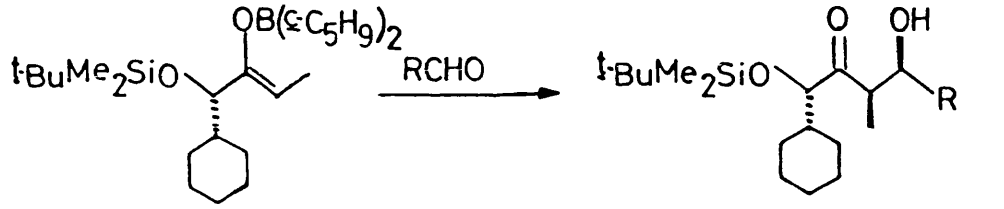


Scheme 31

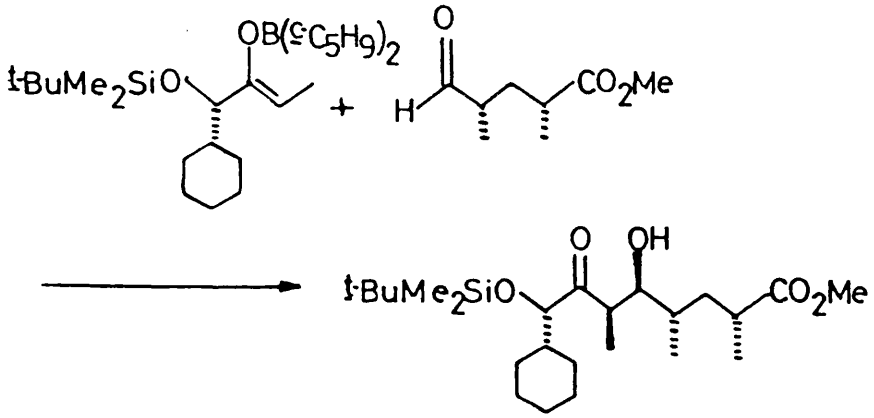
Another enantioselective enolate which has been used in aldol reactions is the chiral α-siloxyethyl ketone (15). Masamune and co-workers[1,33] showed that the boron enolate of this ketone reacts with both chiral and achiral aldehydes to give aldol products of very high diastereomeric purity (Scheme 32). Unfortunately, the conversion of these products to synthetically useful β-hydroxy acids and β-hydroxy aldehydes requires degradation of the chiral auxiliary,[33] (Scheme 33).



(15)



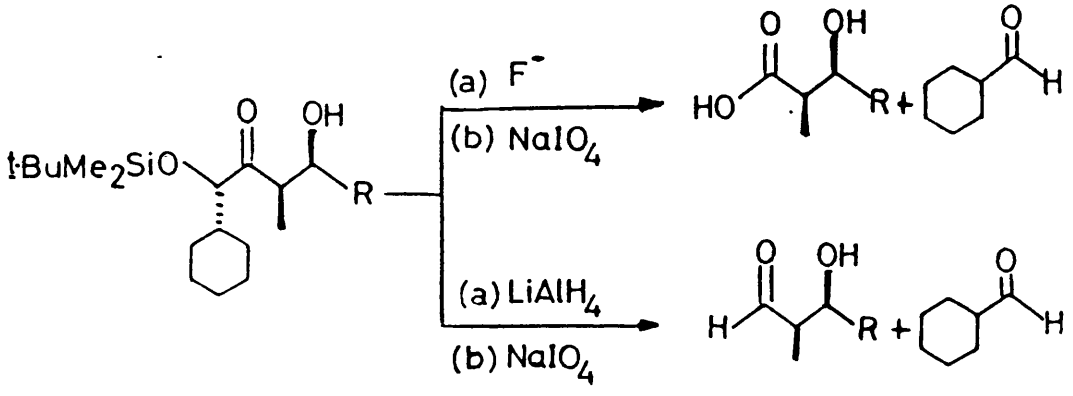
R	diastereomeric purity (%)
t-Bu	>99
Et	>98



diastereomeric purity (%)

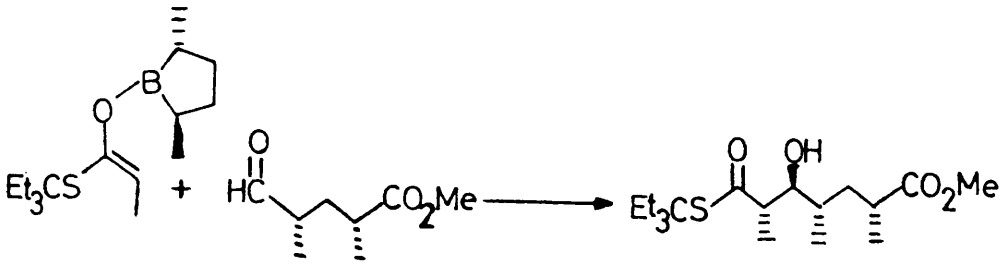
>98

Scheme 32

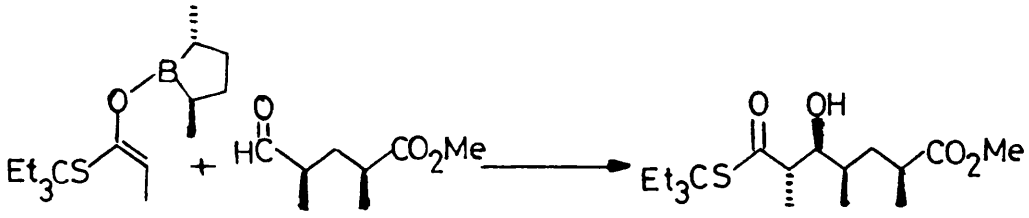


Scheme 33

Masamune and co-workers[34] have recently reported an enantioselective boron enolate (16) in which the chiral inducing moiety resides at the metal centre. This reagent is particularly important, since it represents the first enolate which shows high inherent diastereofacial selectivity and excellent *anti* simple stereoselectivity (Scheme 34).



(16) diastereomeric purity (%)
>99.5



(16) diastereomeric purity (%)
>99.5

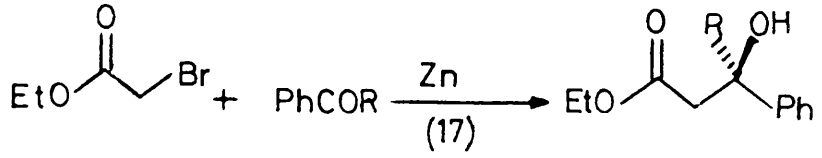
Both reactions performed at -78 °C in pentane

Scheme 34

1.4.4 Chiral complexing agents

There have been several studies of the effect on aldol stereochemistry of chiral auxiliaries which are not covalently bonded to one of the reactants. Guetté and co-workers[35] studied the Reformatsky reaction in the presence of the bidentate ligand

(-)sparteine (17). Depending on the type of carbonyl-active compound used large variations in the enantioselectivity are observed, as shown by the examples cited (benzaldehyde and acetophenone) in Scheme 35, a further disadvantage being that the chemical yields are low (21% and 16% respectively).



R	Optical purity (% ee)	Yield (%)
H	94	21
Me	38	16

Scheme 35

The high diastereofacial preference observed when benzaldehyde was the carbonyl-active compound has been explained in terms of the chelated zinc enolate shown in Figure 14. Inspection of the model shows that one ligand position is more sterically congested than the other. It has been proposed that the aldehyde binds to this site and its conformation is determined largely by interaction with the axial hydrogen at C-3 of the auxiliary.

Seebach and co-workers[36] also examined the effect of chiral complexing agents in aldol reactions. Addition of the tartrate-derived complexing agents (18) and (19) resulted in aldol reactions exhibiting low levels of asymmetric induction, as shown in Schemes 36 and 37 resepctively.

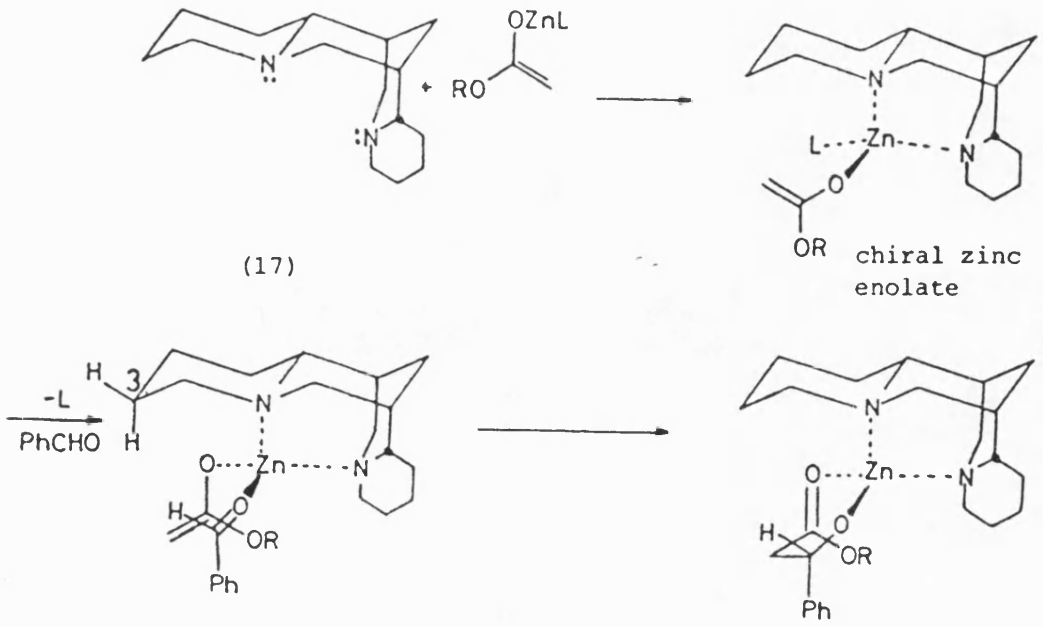
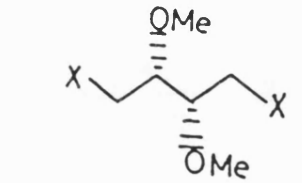
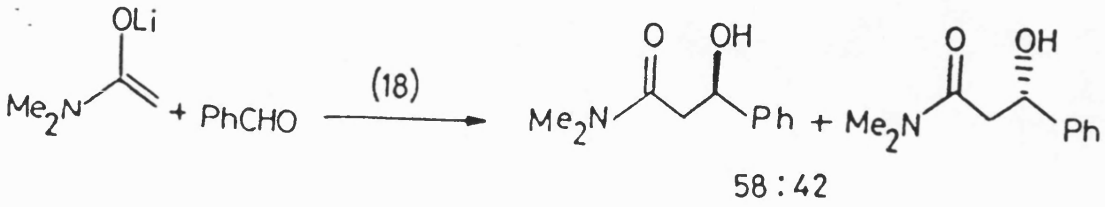


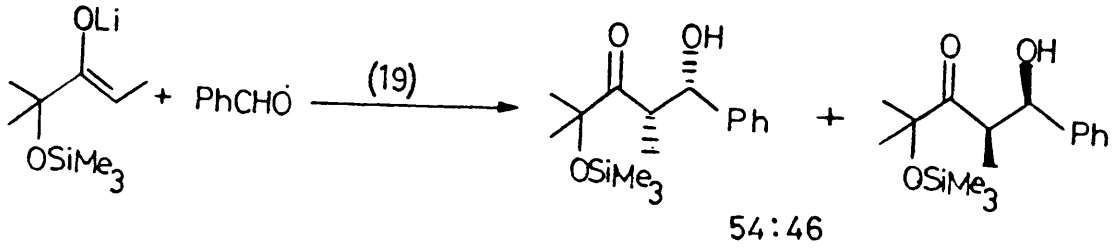
Figure 14



X = NMe$_2$ (18) X = OMe (19)



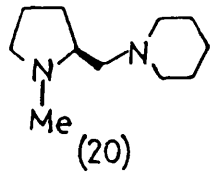
Scheme 36

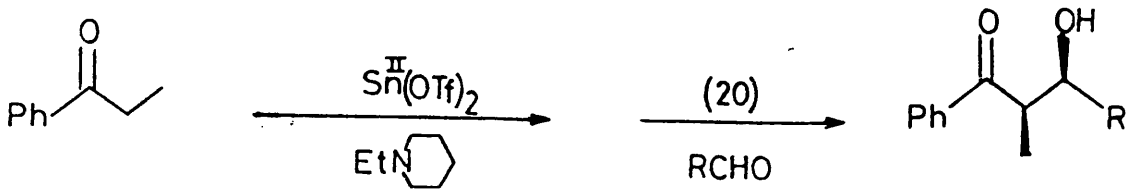


Scheme 37

The best example of chiral complexing agent-induced diastereofacial selectivity has been obtained by Mukaiyama and Iwasawa.[37]

The tin(II) enolate of propiophenone was reacted with a series of achiral aldehydes in the presence of chiral diamine (20) (Scheme 38 and Table 4).





Scheme 38[37]

Table 4

R	*syn/anti* (%)	Optical purity of *syn* diastereoisomer (%ee)	Yield (%)
Ph	86:14	80	74
t-Bu	95:5	90	57
c-C_6H_{11}	80:20	80	63
p-ClC_6H_4	86:14	85	72

Very good levels of asymmetric induction were observed (80-90%). The diastereofacial selectivity observed in the reaction was attributed to the fact that chiral diamine (20) is able to co-ordinate effectively with the stannous ion.

It is clear from the preceding discussion that several good methods are now available for controlling simple diastereoselectivity and diastereofacial selectivity in aldol reactions. We have used some of these techniques, particularly reactions of lithium and silyl enolates, to investigate the regio- and diastereoselectivity in aldol reactions of cyclopent-2-enone and but-2-en-4-olide.

RESULTS AND DISCUSSION

CHAPTER 2

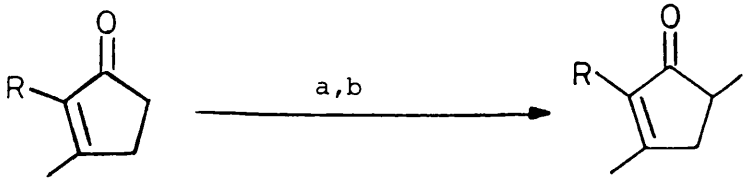
Regio- and Diastereo-Selectivity in the Directed Aldol Reactions of Cyclopent-2-enone

Before disclosing our results on the aldol chemistry of cyclopent-2-enone (1), it is necessary briefly to review some literature precedents for anion reactions of (1).

2.1 Review of the Anion Chemistry of Cyclopent-2-enone

Although (1) is frequently used in natural product synthesis,[38] a systematic study of its regio- and diastereo-selectivity in aldol reactions has until now not been undertaken.

In general, literature references to anion reactions of (1) are scarce. Indeed, it has been reported by Smith and co-workers[39] that (1) undergoes polymerisation in the presence of LDA at -78 °C, and that 3-substituents were necessary for successful anion reactions (Scheme 39), the reason being that they slow the competing base-catalysed self-condensation process.

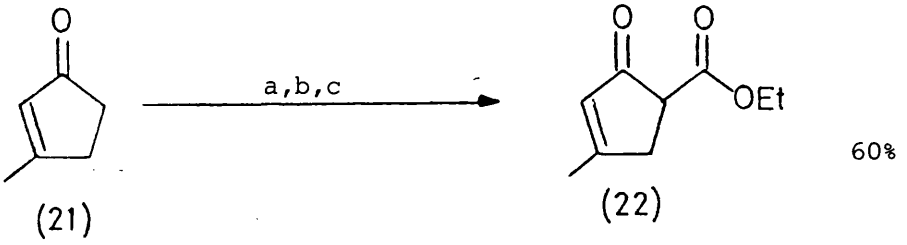


R	(%)
H	56
Me	56

[a]LDA, THF, -78 °C; [b]MeI, -78 °C

Scheme 39

Another anion reaction involving a 3-substituted cyclopent-2-enone has been reported by Fallis and co-workers.[40] 3-Methylcyclopent-2-enone (21) underwent an alkoxycarbonylation reaction with diethylpyrocarbonate to give the 5-ethoxycarbonyl-3-methylcyclopent-2-enone (22) (Scheme 40).



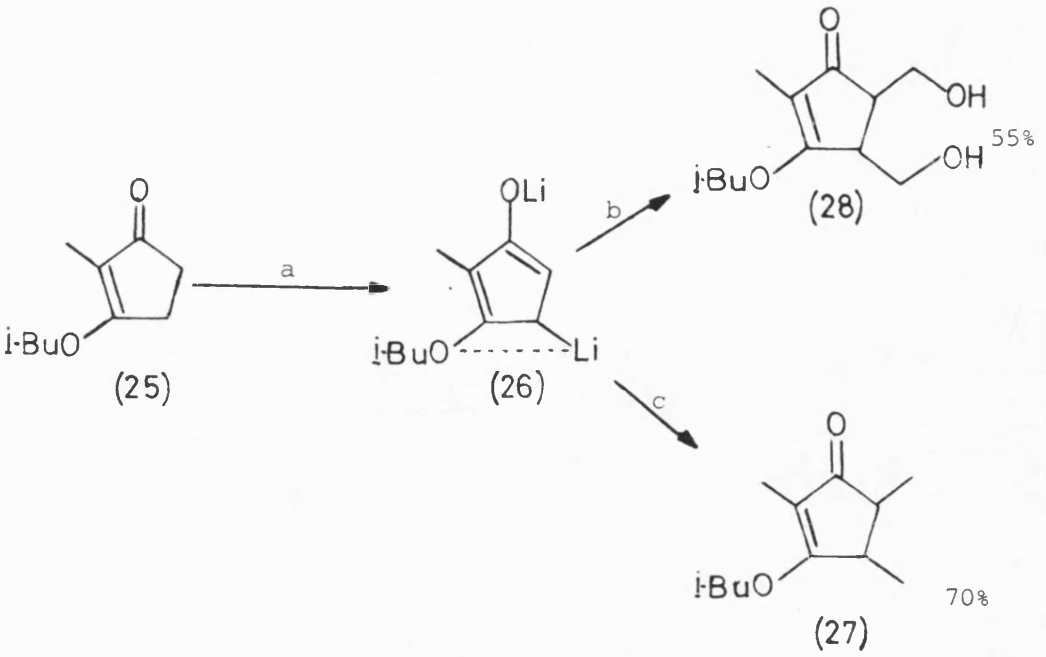
[a]LDA, THF, -78 °C; [b]$(EtOCO)_2O$, -78 °C; [c]H^+, -78 °C.

Scheme 40

The anion reactions depicted in Schemes 39 and 40 suggest that under kinetic conditions, 3-alkylcyclopent-2-enones are deprotonated at C-5 and form cross-conjugated dienolates similar to (23). There have been no literature reports of deprotonation of cyclopent-2-enones at C-4 to give a fully conjugated dienolate system (24).

R = alkyl group

Although there have been few reports on alkylation and aldol reactions of mono-anions of cyclopent-2-enones, Koreeda and co-workers[41a,b] have investigated dianion reactions of 3-alkoxycyclopent-2-enones. 3-Isobutoxy-2-methylcyclopent-2-enone (25), upon treatment with 2.5 equivalents of LDA under kinetic conditions, gave the dianion (26) which underwent efficient methylation and formylation with methyl iodide or methanal to give the 4,5-disubstituted cyclopent-2-enones (27) or (28) respectively (Scheme 41).

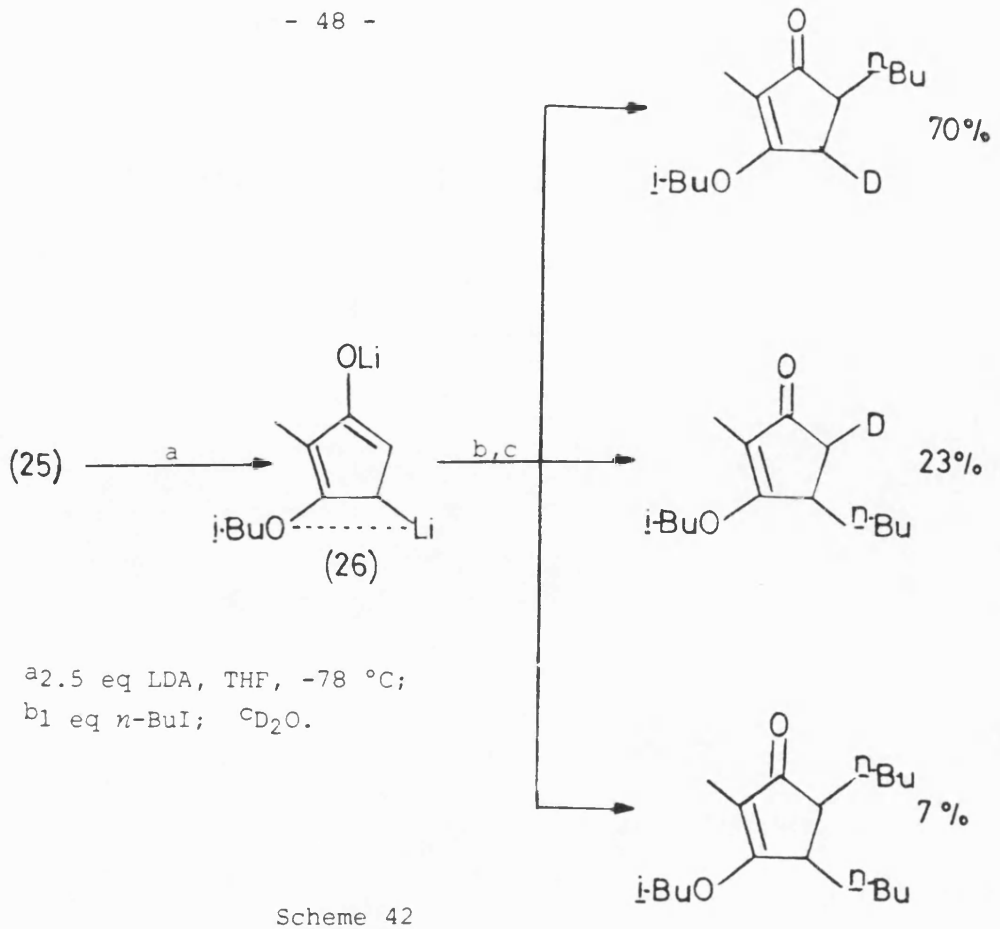


[a]2.5 eq LDA, THF, -78 °C; [b]5 eq HCHO; [c]5 eq MeI

Scheme 41

No information was given on mono-anion reactions of (25), but it was suggested that the dianion (26) initially reacts with electrophiles at C-5, and then undergoes a subsequent reaction at C-4.[41a] For example, when (26) was treated with one equivalent of *n*-butyl iodide at 0 °C, followed by quenching with D_2O, the major product was the 5-alkylated cyclopent-2-enone (Scheme 42). Although the substitution reaction showed only modest regioselectivity, alkylation at C-5 was clearly favoured.

There have been no reports of aldol or alkylation reactions involving cyclopent-2-enones under thermodynamic reaction conditions.



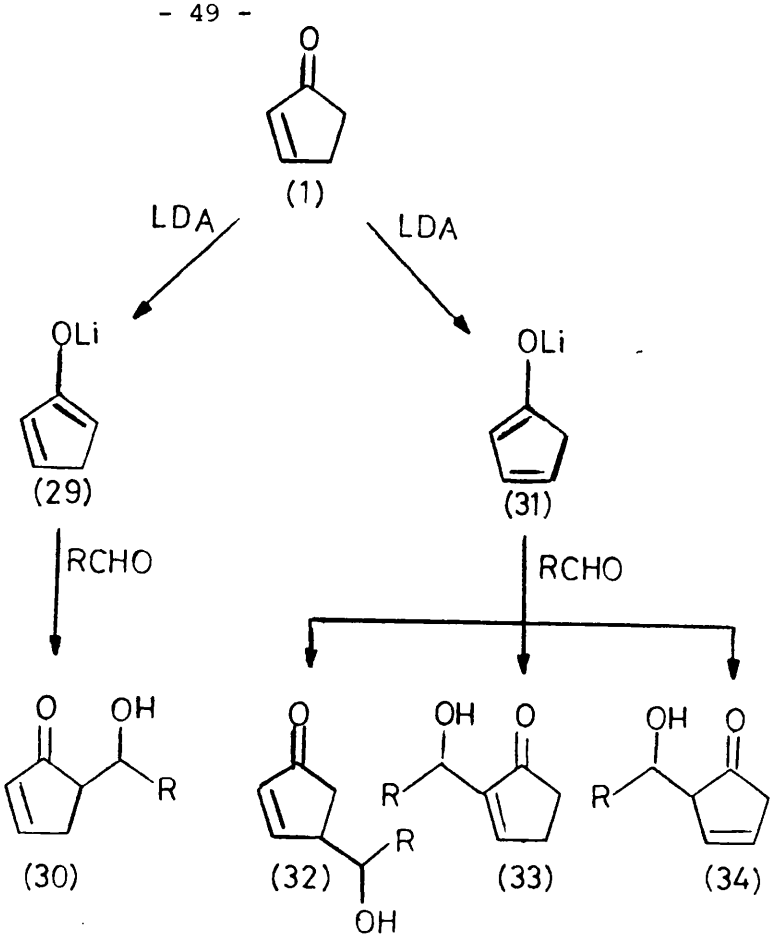
Scheme 42

2.2 Structural Assignment

At the start of this investigation on the aldol chemistry of (1), the regiostructure and relative stereochemistry of many of the aldol products could not be predicted with certainty, so methods for analysing both structural features had to be rigorously determined.

2.2.1 Regiostructure determination

Previous anion reactions of alkylated cyclopent-2-enones (Section 2.1), had suggested that under kinetic conditions (1) would be deprotonated at C-5 and the cross-conjugated dienolate (29) would be formed, which would react with aldehydes to give 5-substituted cyclopent-2-enones (30). However, the possibility of deprotonation of (1) at C-4 to form the fully conjugated dienolate (31) could not be dismissed. The fully conjugated dienolate (31) would be expected to react with aldehydes to give either the 4-substituted cyclopent-2-enone (32), the 2-substituted cyclopent-3-enone (34), or the 2-substituted cyclopent-2-enone (33) (Scheme 43).



Scheme 43

Spectroscopic data on the product from the LDA-mediated aldol reaction of (1) and benzaldehyde are used to demonstrate how the regiostructure of the aldol products were determined.

^{1}H n.m.r. and ^{13}C n.m.r. spectra showed only one regioisomer had been formed and it consisted of a mixture of *syn* and *anti* diastereoisomers. The i.r. spectrum of the diastereomeric mixture showed strong absorptions at 3450 and 1670 cm^{-1} which are characteristic of OH and CO groups respectively, indicating the addition reaction had been successful and a hydroxyketone was produced. The mass spectral (C.I.) data confirmed this observation; an $(M + 1)^{+}$ fragment at m/z 189 showed that the product was a monosubstituted cyclopentenone which could be any of the four aldols shown in Scheme 43 with R = Ph.

Data from the i.r. spectrum favoured aldol structures (30) and (33), because the carbonyl absorption was characteristic of an α,β-unsaturated ketone and the position and shape of the hydroxy absorption was unaffected by an i.r. dilution study (CCl_4), suggesting an intramolecular H-bonded structure. The regioselectivity of the aldol adduct was more confidently assigned by n.m.r. spectroscopy.

The ^{1}H n.m.r. spectrum of the product showed two olefinic resonances characteristic of a conjugated enone system (Table 5). Both olefinic resonances appeared as doublets of triplets. Their splitting pattern and coupling constants were identical to those of the H-2 and H-3 resonances of cyclopent-2-enone (1)[42] and hence a $CO-CH=CH-CH_2$ system was present in the aldol product and addition must have occurred at C-5. The aldol product therefore has structure (30), with R = Ph.

Further evidence of the 5-substituted cyclopent-2-enone assignment comes from ^{13}C n.m.r. spectroscopy (Table 6). The olefinic carbons of the product have very similar chemical shifts and the same multiplicities as the C-2 and C-3 olefinic carbons of (1),[43] hence the product must be either a 4- or 5-substituted cyclopent-2-enone.

The methylene carbon of the product has a similar chemical shift to that of the C-4 methylene of (1) and the chemical shift value of the methine carbon (*ca.* 51.8 ppm) is closer to the calculated chemical shift for a methine carbon of a 5-substituted cyclopent-2-enone (55.7 ppm)[44] than the calculated value for the methine carbon of a 4-substituted cyclopent-2-enone (44.9 ppm),[44] which again indicated that the aldol product has structure (30).

2.2.2 Determination of the relative stereochemistry

The relative stereochemistry of the aldol product was provisionally assigned by measuring the vicinal coupling constant between the methine proton on the cyclopent-2-enone ring (H-5) and the carbinol proton (H-6). It was assumed that the *anti* diastereoisomer would have a larger coupling constant than the *syn* diastereoisomer.

This method of stereostructural analysis has been used by other research groups and is based on the relationship between the dihedral angle ϕ and hence the favoured conformation of the aldol adduct and the coupling constant as derived from the Karplus equation.[2,45]

If it is assumed that there is intramolecular H-bonding between the hydroxylgroup and the carbonyl group in the aldol product (position and shape of hydroxy absorption unchanged by i.r. dilution

Table 5

^{1}H N.m.r. chemical shifts and multiplicities of H-2 and H-3 resonances in cyclopent-2-enone (1) and typical aldol product

Chemical shift δ_H (ppm) and multiplicities (Hz)			
Resonance	Cyclopent-2-enone[42] (1)	Aldol product	
		Major diastereoisomer	Minor diastereoisomer
H-2	6.11, dt, (6.0, 2.0)	6.12, dt, (6.0, 2.0)	6.08, dt, (6.0, 2.0)
H-3	7.63, dt, (6.0, 2.5)	7.60, dt, (6.0, 2.5)	7.66, dt, (6.0, 2.5)

Table 6

^{13}C N.m.r. chemical shifts of ring carbons in (1) and typical aldol product

Chemical shift δ_C (ppm) and multiplicities			
Resonance	Cyclopent-2-enone[43] (1)	Aldol product	
		Minor isomer	Major isomer
C-1	210.7, s	211.0, s	212.6, s
C-2	134.4, d	133.9, d	133.6, d
C-3	165.3, d	166.1, d	165.2, d
C-4	29.1, t	29.6, t	32.6, t
C-5	34.1, t	52.2, d	50.8, d

Footnote: multiplicites refer to off-resonance spectrum [s = singlet (C), d = doublet (CH), t = triplet (CH_2)]

study), then of the three possible staggered conformations for the *syn* and *anti* cyclopent—2—enone aldols (Figure 15), conformations in which intramolecular H-bonding is strongest are favoured. These conformations are A for the *syn* aldol and A' for the *anti* aldol. Since the dihedral angle for these two conformations are 60° and 180° respectively, then according to the Karplus equation, coupling constant $J_{5,6anti} > J_{5,6syn}$

Based on this method of stereostructural analysis, the major diastereoisomer from the LDA-mediated reaction of (1) and aldehydes was provisionally assigned the *anti* relative stereochemistry (see Experimental Section and Table 13).

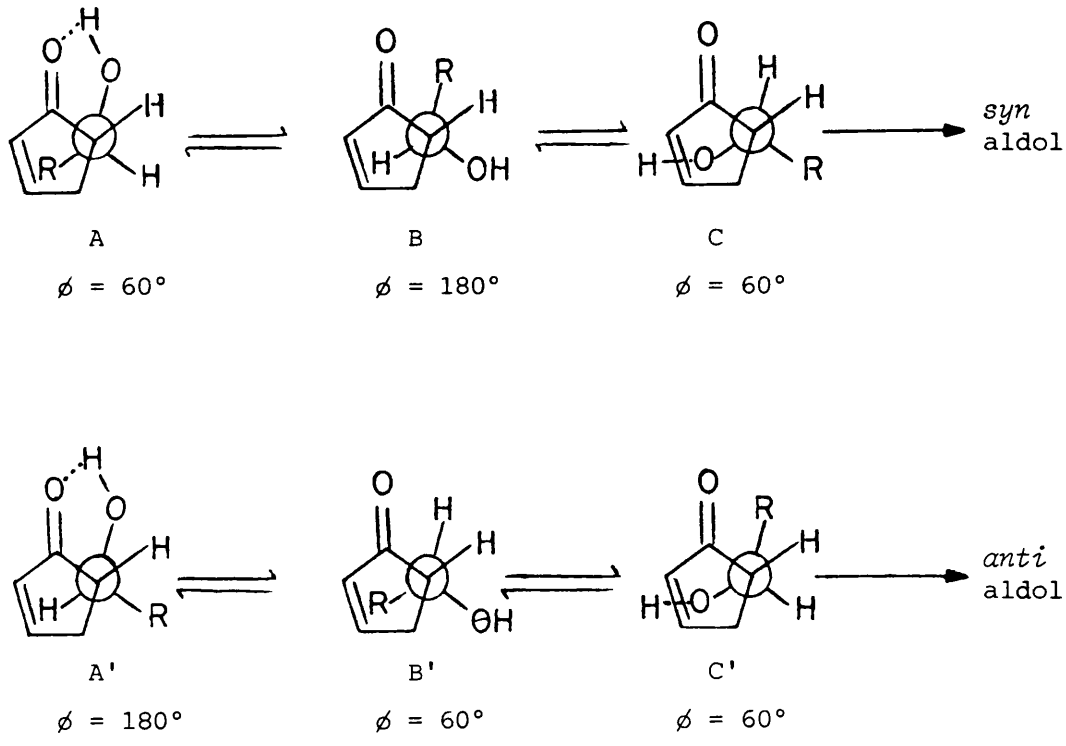
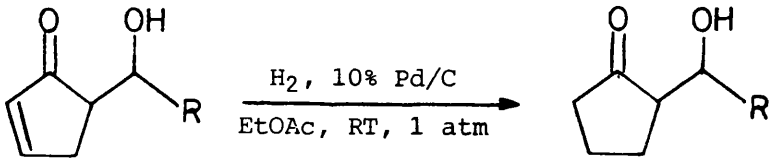


Figure 15

Although vicinal coupling constants $J_{5,6}$ were useful, they could not be used to determine the relative stereochemistry of all the aldol products because the carbinol resonance (H-6) and ring methine resonance (H-5) often appeared as complex multiplets and hence $J_{5,6}$ could not be estimated.

Unequivocal proof of the relative stereochemistry of the 5-substituted cyclopent-2-enone aldol was instead achieved by chemical correlation with 2-substituted cyclopentanones of known stereochemistry. Selected 5-substituted cyclopent-2-enones obtained from the aldol reaction of (1) with achiral aldehydes (see Table 11 in Section 2.3.2) were catalytically reduced to their corresponding 2-substituted cyclopentanones (Scheme 44).



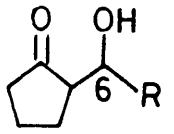
R		R		Yield (%)
Ph	(35)	Ph	(38)	95
$PhCH_2$	(36)	$PhCH_2$	(39)	93
Me	(37)	Me	(40)	91

Scheme 44

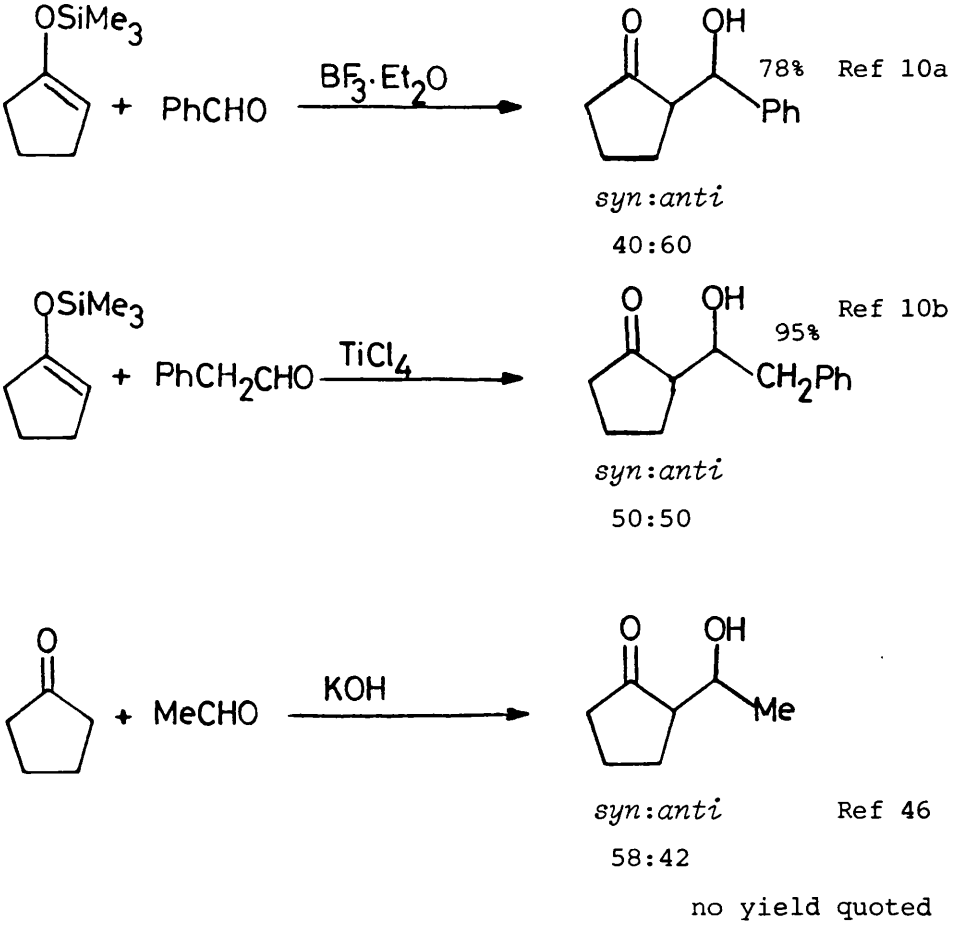
Comparison of the ^1H n.m.r. data of the hydrogenation products (38), (39) and (40) with literature data on *syn* and *anti* diastereoisomers of 2-substituted cyclopentanones which had been prepared by the addition reactions shown in Scheme 45, confirmed our earlier assumption that the major diastereoisomer from aldol reactions of the lithium dienolate (29) and achiral aldehydes have *anti* relative stereochemistry (Table 7). The relative stereochemistry of the cyclopentanone aldol adducts shown in Scheme 45 was assigned on the basis of $J_{2,6}$ coupling constants taken from their ^1H n.m.r. spectra.

Table 7

^1H N.m.r. chemical shifts (ppm) of carbinol resonance (H-6) in 2-substituted cyclopentanones



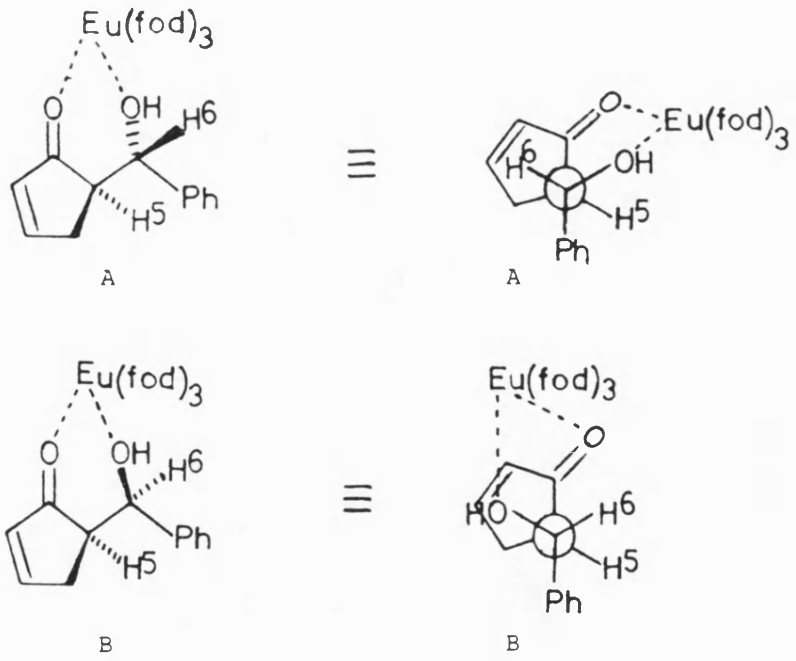
Group	Chemical shift δ_H (ppm)				
	Saturated aldol			Literature compound	
R	Major isomer	Minor isomer		*anti* isomer	*syn* isomer
Ph	4.69	5.26	(38)	4.68[10a]	5.16
$PhCH_2$	3.90	4.32	(39)	3.85[10b]	4.36
Me	3.85	4.26	(40)	3.75[46]	4.14



Scheme 45

Although chemical correlation was the best and most accurate method of determining the relative stereochemistry of the aldol products, a lanthanide shift study using $Eu(fod)_3$ also provided some information on the relative stereochemistry of the 5-substituted cyclopent-2-enones.[47]

The lanthanide shift study was performed on aldol (35), and the results of this study are listed in Table 8. The data listed in this table indicate good linearity for both the major and minor diastereoisomers in the concentration range used in the experiment. The major diastereoisomer experienced stronger paramagnetic induced shifts than the minor diastereoisomer, which suggests that there is stronger bonding to the lanthanide atom and a more stable lanthanide-aldol complex is formed. The paramagnetic induced shifts are strongest at protons H-5 and H-6, indicating that there is probably bidentate ligation to the lanthanide metal from the alcohol and carbonyl oxygens, so complexes analogous to those depicted in Figure 16 are produced.

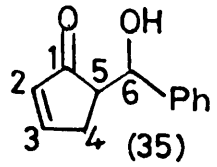


Lanthanide-aldol complexes derived from aldol (35) and $Eu(fod)_3$

Figure 16

Table 8

Lanthanide shift study on 5-(1'-hydroxyphenylmethyl)cyclopent-2-enone (35)



(35)

[Eu(fod)$_3$]/[substrate]	Chemical shifts δ_H (ppm)											
	Major diastereoisomer						Minor diastereoisomer					
	H-2	H-3	H-4a	H-4b	H-5	H-6	H-2	H-3	H-4a	H-4b	H-5	H-6
0	6.12	7.60	2.42	2.18	2.64	4.58	6.08	7.66	2.32	2.68	2.58	5.25
44 x 10^{-3}	6.60	7.78	2.90	2.73	3.64	5.72	6.29	7.78	2.51	2.90	2.88	5.59
99 x 10^{-3}	7.06	7.92	3.32	3.30	4.80	6.92	6.43	7.82	2.62	3.04	3.20	5.88
191 x 10^{-3}	7.75	8.11	4.18	4.00	6.40	9.60	6.68	7.93	2.86	3.35	3.82	6.50
Intercept	6.25	7.68	2.50	2.34	2.90	4.63	6.17	7.72	2.38	2.70	2.60	5.28
Slope $Gc_{Eu(fod)_3}$(ppm)	7.75	7.30	8.70	8.33	18.31	22.96	2.86	0.91	2.60	3.45	6.35	6.50

In complex A, derived from the *anti* aldol, proton H-5 is on the same face of the aldol as the binding site to the europium atom and hence would be expected to experience a strong $\Delta\delta$ value. In complex B, derived from the *syn* aldol, proton H-5 is on the opposite face to the binding site of the aldol and thus would be expected to experience a smaller $\Delta\delta$ value.

Inspection of Table 8 reveals that the H-5 resonance of the major diastereoisomer has a slope (G-value) of 18.31 ppm and the H-5 resonance of the minor diastereoisomer has a slope of 6.35 ppm. On this basis, the major diastereoisomer from the aldol reaction of lithium dienolate (29) and benzaldehyde would have *anti* relative stereochemistry.

2.3 Aldol Reaction of Cyclopent-2-enone under Kinetic Conditions (LDA-mediated)

Most of the pioneering work on stereoselectivity of the directed aldol reaction was carried out using kinetic conditions and employing lithium amide bases.[4a,4b]

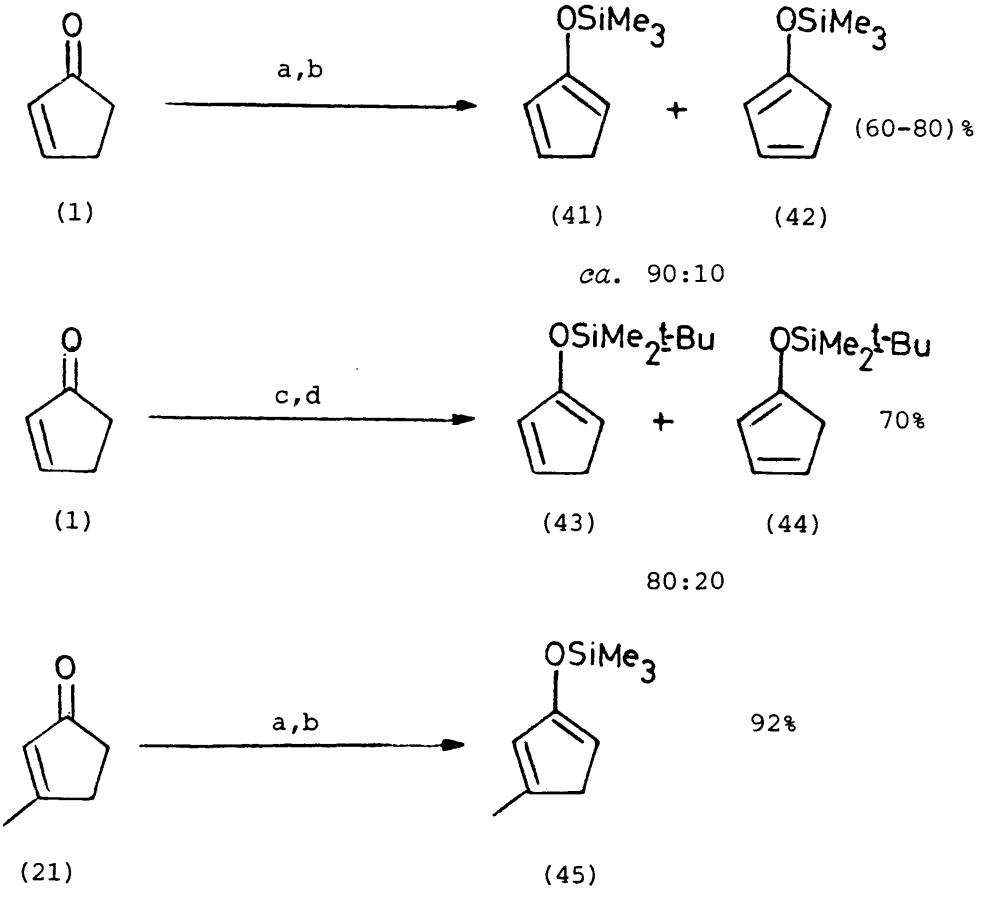
To begin our investigation of the aldol chemistry of (1), it was decided to use similar conditions and examine:

(i) The structure of the kinetic dienolate of (1);
(ii) the regio- and diastereo-selectivity of the LDA-mediated aldol reaction of (1); and
(iii) variations in the diastereoselectivity of the aldol reaction of (1) with time.

2.3.1 Enolisation of cyclopent-2-enone under kinetic conditions

It was mentioned in Section 2.2.1 that enolisation of (1) can result in the formation of a cross-conjugated or fully conjugated dienolate. To determine which of these is favoured under kinetic conditions the lithium dienolates derived from cyclopent-2-enones (1) and (21) were quenched with silylating agents at -78 °C (Scheme 46).

Under kinetic conditions the cross-conjugated silyl dienolates (41), (43) and (45) were favoured.[48] Smaller amounts (10-20%) of the fully conjugated silyl dienolates (42) and (44) were also formed from (1), but no fully conjugated siloxycyclopentadiene was produced



Yields refer to mixture of regioisomers

[a]LDA, THF, -78 °C, 40 min; [b]Me_3SiCl, -78 °C → RT;

[c]LDA, THF-HMPA, -78 °C, 40 min; [d]t-$BuMe_2SiCl$, -78 °C → RT

Scheme 46

from 3-methyl cyclopent-2-enone (21). No C-silylated products were isolated.

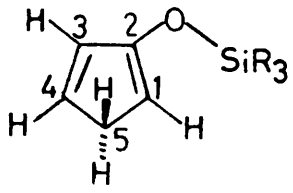
All the siloxycyclopentadienes shown in Scheme 46 had spectral data consistent with their proposed structures. For example, the

mass spectral data (E.I.) of mixture (41) and (42) showed a $M^{+\cdot}$ at m/z 154, mixture (43) and (44) showed a $M^{+\cdot}$ at m/z 196 and silyl dienolate (45) exhibited a (M+1) fragment at m/z 169, in its (C.I.) mass spectrum.

Selected ^{1}H n.m.r. and ^{13}C n.m.r. data on the aforementioned siloxycyclopentadienes are cited in Tables 9-11. The ^{1}H n.m.r. data were particularly useful in determining the regiostructure of the silyl dienolate. For instance, the ^{1}H spectra of the cross-conjugated silyl dienolates (41) and (43) showed two low field olefinic resonances at *ca.* δ 6.4 and δ 6.3 and one high field olefinic resonance at *ca.* δ 5.3, which indicated that only the proton bonded to carbon atom C-1 was in conjugation with the siloxy moiety. In contrast to this, the ^{1}H spectra of the fully conjugated siloxy-dienes (42) and (44) showed one low field olefinic resonance at *ca.* δ 6.3 and two high field olefinic resonances at *ca.* δ 5.7 and *ca.* δ 5.4, indicating that the protons bonded to carbon atoms C-2 and C-4 were in conjugation with the siloxy moiety.

Table 9

^{1}H N.m.r. and ^{13}C n.m.r. data on cross-conjugated siloxycyclo-pentadienes (41) and (43)



Coupling constants for ring protons (±0.5 Hz)

$J_{1,3}$ = 2.0 $J_{3,4}$ = 5.5

$J_{1,4}$ = 2.0 $J_{3,5}$ = 1.5

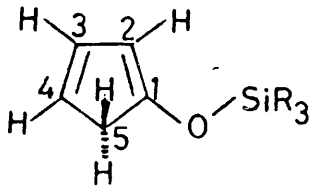
$J_{1,5}$ = 2.0 $J_{4,5}$ = 2.0

$R_3 = Me_3$ (41); $R_3 = t\text{-}BuMe_2$ (43)

Chemical shift (ppm)					
^{1}H Resonance	(41)	(43)	^{13}C Resonance	(41)	(43)
H-1	5.28, p	5.26, p	C-1	104.1	104.4
H-2	-	-	C-2	156.4	156.6
H-3	6.41, ddt	6.38, ddt	C-3	131.9	132.1
H-4	6.30, dq	6.28, dq	C-4	133.7	133.4
H-5	2.97, td	2.93, td	C-5	37.8	37.6

Table 10

^1H N.m.r. and ^{13}C n.m.r. data on fully conjugated siloxycyclopentadienes (42) and (44)



Coupling constants for ring protons (±0.5 Hz)

$J_{2,3}$ = 2.0 $J_{3,4}$ = 5.5

$J_{2,4}$ = 1.5 $J_{3,5}$ = 2.0

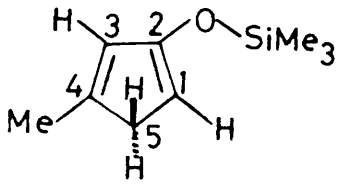
$J_{2,5}$ = 1.5 $J_{4,5}$ = 1.5

R_3 = Me_3 (42); R_3 = *t*-$BuMe_2$ (44)

Chemical shift (ppm)					
^1H Resonance	(42)	(44)	^{13}C Resonance	(42)	(44)
H-1	-	-	C-1	161.9	162.2
H-2	5.41, dq	5.39 dq	C-2	106.2	106.3
H-3	6.33, dtd	6.32, dtd	C-3	131.8	131.9
H-4	5.73, dq	5.71, dq	C-4	120.0	120.1
H-5	2.90, td	2.88, td	C-5	41.0	41.0

Table 11

^1H N.m.r. and ^{13}C n.m.r. data on cross-conjugated siloxycyclopentadiene (45)



(45)

Coupling constants for ring protons (±0.5 Hz)

$J_{1,3}$ = 2.0; $J_{3,5}$ = 1.0

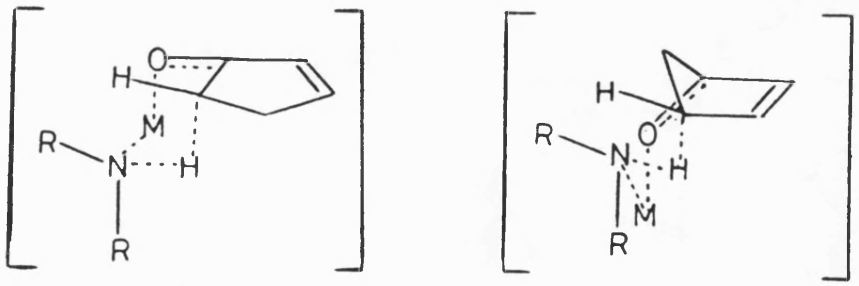
$J_{1,5}$ = 2.0; $J_{3,Me}$ = 1.5

Chemical shift (ppm)			
^1H Resonance	(45)	^{13}C Resonance	(45)
H-1	4.98, q	C-1	101.4
H-2	-	C-2	155.8
H-3	5.83, m	C-3	126.8
H-4	-	C-4	145.3
H-5	2.76, dd	C-5	41.0
Me	1.98, d	Me	16.5

The ratio of cross-conjugated silyl dienolate to fully conjugated silyl dienolate was estimated by comparing integrals in their ^1H n.m.r. spectra. To our knowledge, this is the first report of the preparation of fully conjugated dienolates of cyclopent-2-enones. Fully conjugated dienolates of cyclohex-2-enones are known.[49] Attempts to separate the cross-conjugated silyl dienolate from the fully conjugated silyl dienolate were unsuccessful. Distillation and chromatography only resulted in mixtures of the two regioisomers.

The regioselectivity of enolisation described in the foregoing discussion may have resulted because deprotonation at C-5 is favoured, since it can proceed *via* the low energy chair transiton state A depicted in Figure 17.

The small amounts of the kinetically less favoured fully conjugated silyl dienolate may have been formed by either deprotonation of (1) at C-4 *via* the cyclic transition state B, or *via* an alternative acyclic transition state or by equilibration with the cross-conjugated dienolate (see Section 2.4.1 for more details). Equilibrations between cross-conjugated lithium dienolates and fully conjugated lithium dienolates are known for cyclohex-2-enone systems.[50]



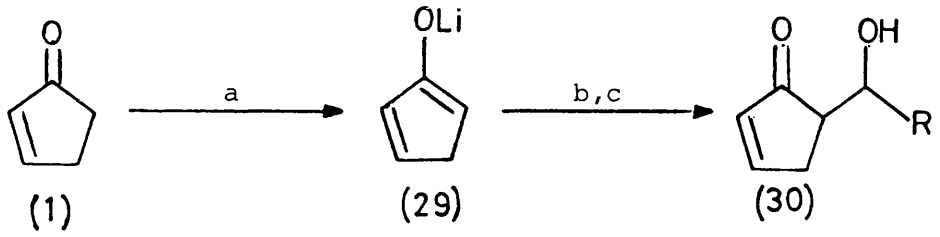
A favoured B unfavoured

Figure 17

Under kinetic conditions (1) reacts with strong lithium bases to give predominantly the cross-conjugated dienolate (29). We next examined the aldol reaction of this dienolate with prochiral aldehydes.

2.3.2 Regio- and diastereo-selectivity in aldol reactions involving lithium dienolates of cyclopent-2-enone

The results of a study on the aldol reaction between the lithium dienolate of (1) and a series of achiral aldehydes under kinetic conditions are shown in Scheme 47 and Table 12.[51]



[a]LDA, THF, -78 °C; [b]RCHO, -78 °C; [c]NH_4Cl-H_2O, -78 °C.

Scheme 47

Table 12

Aldehyde RCHO[a]	Aldol product		
	Diastereoisomer ratio[b] *anti* *syn*	Yield[c] (%)	Compound[d]
MeCHO	68 : 32	63	(37)
EtCHO	76 : 24	66	(46)
$Me(CH_2)_4CHO$	83 : 17	73	(47)
$Me(CH_2)_9CHO$	81 : 19	72	(48)
Me_2CHCHO	94 : 6	80	(49)
Me_3CCHO	98 : 2	83	(50)
PhCHO	74 : 26	71	(35)
$PhCH_2CHO$	84 : 16	69	(36)

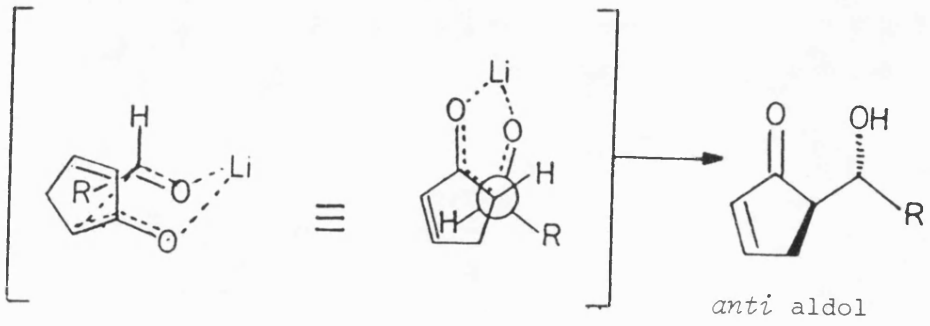
[a]Diastereomeric ratios and yields refer to typical values. Each aldol addition was performed more than once.

[b]Diastereomeric ratio analysed by g.l.c. (internal standard) and/or ^{13}C n.m.r. (comparison of the heights of carbinol signal of each stereoisomer).

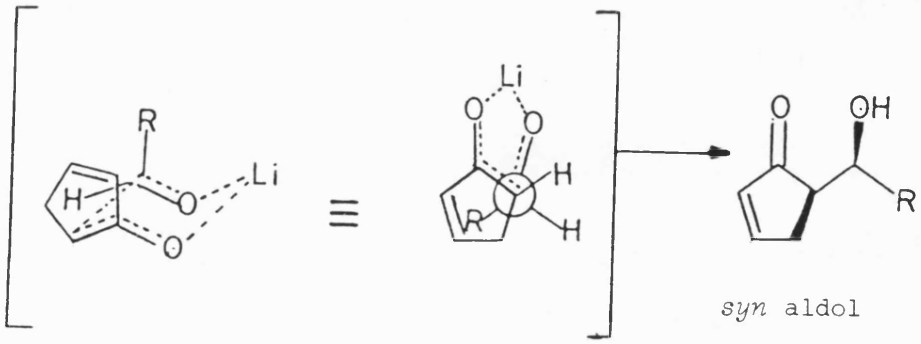
[c]Yield refers to isolated diastereomeric mixture after separation from unreacted aldehyde and polymeric material.

[d]Separation of diastereomeric mixture by chromatography resulted in a smaller recovery of *syn* and *anti* diastereoisomers.

All the aldol reactions were regiospecific and only 5-substituted cyclopent-2-enones were produced. The addition reactions also showed good *anti* diastereoselectivity. The cross-conjugated lithium dienolate (29) is formed under kinetic conditions and it is thought that this reacts with achiral aldehydes *via* a metal-chelated six-centred transiton state[8,52] (Figure 18).



(a)



(b)

Figure 18

The *anti* diastereoselectivity observed in the reaction would result if transition state (a) leading to the *anti* diastereoisomer is favoured over transition state (b) leading to the *syn* diastereoisomer. In transition state (b) there is a destabilising diaxial interaction between substituent R and the cyclopentadiene ring. The level of diastereoselectivity shown in the aldol reaction increases with the steric bulk of the substituent R on the aldehyde.

The regiospecificity of the reaction results because the cross-conjugated dienolate (29) is favoured under kinetic conditions. Any fully conjugated dienolate produced is in equilibration with (29) and prefers to react with aldehydes *via* the chelated transiton states shown in Figure 18.

All the 5-substituted cyclopent-2-enone aldols had spectral data consistent with their proposed structures [*e.g.*, i.r. 3400 (OH), 1670 (CO, conjugated enone) and 1580 cm^{-1} (C=C, conjugated enone)]. For information on how the regio- and stereo-structure of the aldols was determined, see Sections 2.2.1 and 2.2.2. Tables 13 and 14 are used to correlate selected ^{1}H n.m.r. and ^{13}C n.m.r. data on the *syn* and *anti* diastereoisomers of 5-substituted cyclopent-2-enone aldols.

Several trends emerge in comparing the ^{1}H and ^{13}C n.m.r. spectra of the two series of diastereoisomers. The most notable trends from a diagnostic point of view are as follows:

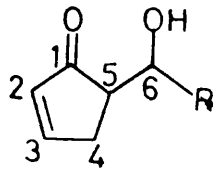
(i) In the ^{13}C spectra, the C-4 and C-6 resonances of the *anti* diastereoisomers occur at higher chemical shift values than their corresponding *syn* diastereoisomers ($\delta_{C_4}anti > \delta_{C_4}syn$ by *ca.* 2-3 ppm and $\delta_{C_6}anti > \delta_{C_6}syn$ by *ca.* 2-4 ppm).

(ii) In the ^{1}H spectra, the H-6 resonance of the *anti* diastereoisomer is at higher field than its *syn* diastereoisomer ($\delta_{H_6}syn > \delta_{H_6}anti$). The *anti* diastereoisomers have H-6 resonances between δ(3.44-4.06) ppm and the *syn* diastereoisomers had H-6 resonances between δ(4.16-4.43) ppm.

Aldol (35) represents an understandable exception to this rule, the anisotropic effect of the phenyl substituent shifts the H-6 resonance of both the *syn* and *anti* diastereoisomers to

Table 13

^{13}C N.m.r. chemical shift in 5-substituted cyclopent-2-enones

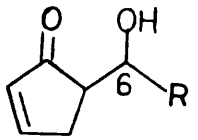


Group R	Chemical shift δ_C (ppm)											
	anti diastereoisomer						*syn* diastereoisomer					
	C-1	C-2	C-3	C-4	C-5	C-6	C-1	C-2	C-3	C-4	C-5	C-6
Me	213.2	133.8	165.2	32.4	50.8	68.5	211.9	134.3	165.8	30.4	51.5	66.4
Et	212.8	133.4	164.8	32.1	48.9	72.8	211.9	133.8	165.3	30.3	49.8	71.1
$Me(CH_2)_4$	213.4	133.7	164.8	32.5	49.4	72.1	211.6	134.2	165.4	30.2	50.4	70.1
$Me(CH_2)_9$	213.5	133.8	164.7	32.6	49.4	72.2	212.2	134.4	165.7	30.1	50.4	70.2
$(Me)_2CH$	214.2	133.8	164.8	32.7	47.4	76.3			*a*			
Me_3C	214.6	133.3	165.1	35.8	45.7	79.9			*a*			
Ph	212.6	133.6	165.3	32.6	50.8	75.2	211.0	133.9	166.1	29.6	52.2	71.2
$PhCH_2$	212.8	134.0	164.9	32.9	48.5	73.1	211.3	134.3	165.3	32.0	49.7	71.2

[a]No spectral data available on *syn* diastereoisomers.

Table 14

^{1}H N.m.r. chemical shifts of the carbinol resonance (H-6) in 5-substituted cyclopent-2-enones



Group R	Chemical shift δ_H (ppm) and ($J_{5,6}$ coupling constant, Hz)	
	anti diastereoisomer	*syn* diastereoisomer
Me	3.88 (9.5)	4.32[b]
Et	3.70 (10.5)	4.22[b]
$Me(CH_2)_4$	3.72[b]	4.18[b]
$Me(CH_2)_9$	3.70[b]	4.16 (3.5)
Me_2CH	3.50 (9.5)	*a*
Me_3C	3.44 (9.5)	*a*
Ph	4.58 (9.5)	5.28 (3.0)
$PhCH_2$	4.03[b]	4.43[b]

[a]No spectral data available for the *syn* diastereoisomer.

[b]Carbinol resonance appears as a complex multiplet, $J_{5,6}$ coupling constant could not be evaluated.

lower field.

The $J_{5,6}$ coupling constants of the *anti* diastereoisomers which could be estimated were all between 9.5 and 10.5 Hz.

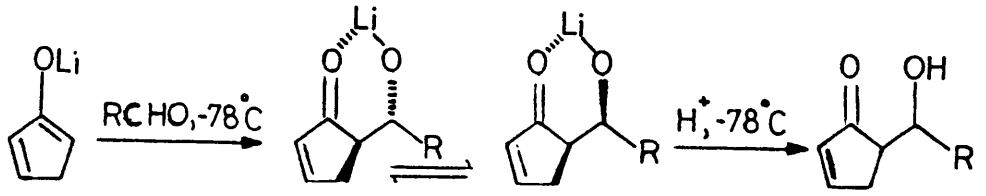
2.3.3 Influence of reaction time on diastereoselectivity of LDA-mediated aldol reactions

It was of interest to see what effect longer reaction times would have on the diastereoselectivity of the LDA-mediated aldol reactions of (1). It was thought that longer reaction times would result in an equilibration between the initially formed *syn* and *anti* aldolates, thus increasing the yield of the *syn* diastereoisomers.

This study was performed by a colleague.[53]

In one experiment, the lithium dienolate (29) was generated under kinetic conditions and then left to react with aldehydes at -78 °C for varying reaction times before being quenched with saturated ammonium chloride (Scheme 48).

The results of this first experiment are listed in Table 15.



(29)

syn/anti mixture

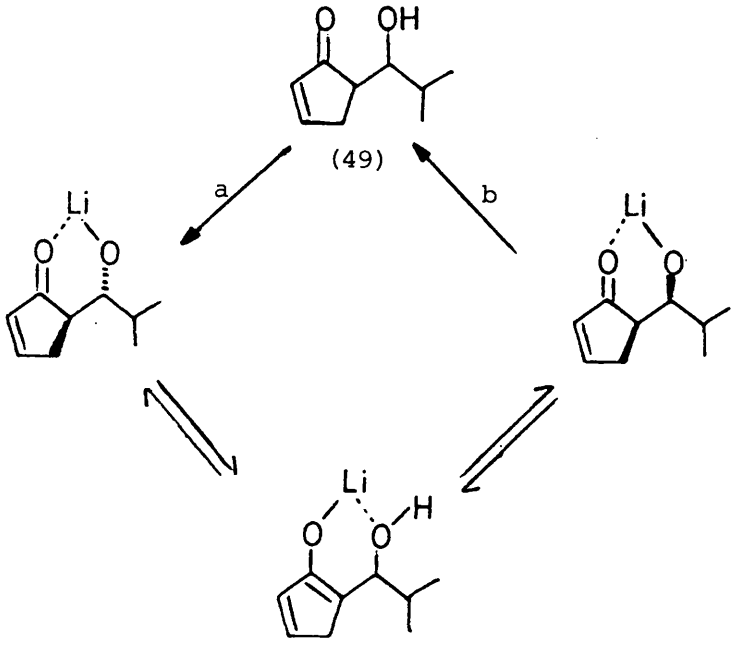
Scheme 48

Table 15

Aldehyde RCHO	Equilibration time (min)	Aldol product		
		anti *syn*[a]	Yield (%)	Compound
MeCHO	10 25	75 : 25 68 : 32	67 86	(37)
EtCHO	1 50	74 : 26 76 : 24	45 66	(46)
PhCHO	60 100	74 : 26 72 : 28	71 73	(35)

[a]Ratio determined by g.l.c. analysis

In a second experiment, the cyclopent-2-enone aldol (49) of known *anti*:*syn* composition was treated with one equivalent of LDA at -78 °C and the resulting lithium aldolate was left to equilibrate. Samples were taken at varying time intervals and the *anti*:*syn* composition was analysed by g.l.c. (Scheme 49, Table 16).



[a]LDA, THF, -78 °C; [b]NH_4Cl-H_2O, -78 °C.

Scheme 49

Table 16

Initial composition[a] *anti* : *syn*	Reaction conditions Time (min)	Temp (°C)	Final composition[a] *anti* : *syn*
94 : 6	60	-78	89 : 11
94 : 6	270	-78	85 : 15
94 : 6	330	-78 → RT	50 : 50[b]

[a]Ratios determined by g.l.c. analysis.

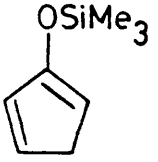
[b]Very low recovery of (49), polymeric material major product.

Only small changes in the *anti*:*syn* composition were observed when the reaction was kept at -78 °C for varying reaction times. If equilibration is taking place, then it is proceeding at a slow rate at -78 °C. When shorter reaction times were employed, the diastereoselectivity of the aldol reaction improved slightly, but at the expense of the overall yield. When the reaction mixture was allowed to warm to room temperature before quenching, it appeared that equilibration was taking place at a faster rate, but polymerisation of the aldolate became a problem. Since only small amounts (*ca.* 10%) of the aldol (49) were recovered, preferential decomposition of one diastereoisomer could account for the large change in the *anti*:*syn* composition. The equilibration between the *syn* and *anti* lithium aldolates is proceeding by either a base catalysed enolisation process or a reverse-aldol process (see Section 1.3.1).

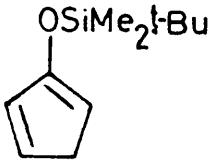
The aldol reactions so far discussed have been regiospecific and the reactions have shown good *anti* diastereoselectivity. To extend the synthetic utility of the cyclopent-2-enone aldol reaction, a method of forming *syn* cyclopent-2-enone aldols in good yield was required and also a method of changing the regioselectivity of the addition reaction. It was thought that both these goals might be achieved *via* aldol reactions of enolsilanes derived from (1).

2.4 *Aldol Reactions of the Silyl Dienolate of Cyclopent-2-enone

During the last decade, there has been a resurgence of interest in the aldol reaction, especially the investigation of its stereochemistry *via* Lewis acid-[10] and fluoride ion-[11] mediated reactions of enolsilanes (see Section 1.2.3). In order to further our investigation of the aldol chemistry of (1), the cross-conjugated silyl dienolates (41) and (43) were prepared and reacted with aldehydes under Lewis acid- and fluoride ion-mediated reaction conditions.



(41)



(43)

2.4.1 Preparation of silyl dienolates of cyclopent-2-enone

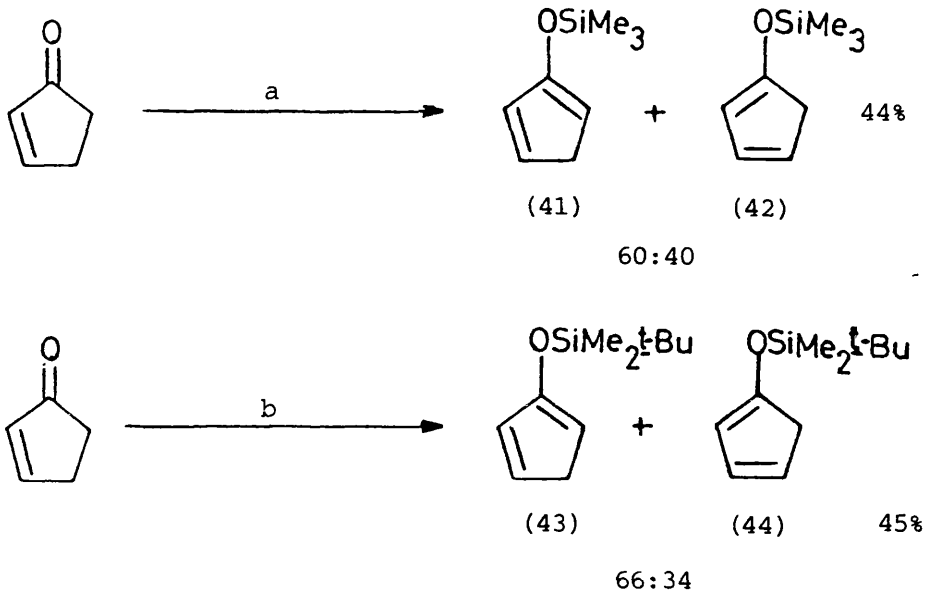
Although there have been a few scattered reports on the use of 2-(trimethylsiloxy)cyclopenta-1,3-diene (41) in synthesis,[48] no information was given on how (41) was prepared.

In our hands, the cross-conjugated silyl dienolates (41) and (43) have been efficiently prepared under kinetic conditions (Section 2.3.1, Scheme 46) and thermodynamic conditions (Scheme 50). In both preparations, the product isolated consisted of mixtures of cross-conjugated and fully conjugated silyl dienolates. A greater proportion of the fully conjugated regioisomer was formed under equilibrating conditions.

The mechanism by which the cross-conjugated silyl dienolates (41) and (43) and fully conjugated silyl dienolates (42) and (44) might have been formed is outlined in Scheme 51.

The cross-conjugated silyl dienolates are formed from their corresponding lithium dienolates, whilst the fully conjugated silyl dienolates are produced by either enolisation of (1) at C-4 [pathway (a) in Scheme 51] or alternatively *via* enolisation of (1) at C-5 to

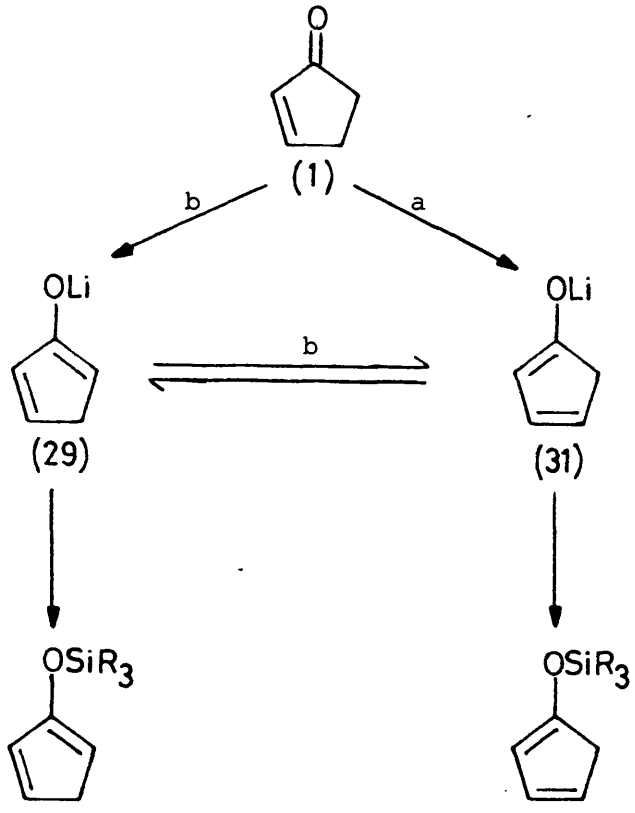
*Part of this work was performed in collaboration with Mr. Xiao-an Zhang.



Yields refer to mixtures of the regioisomers

[a] Me_3SiCl, Et_3N, DMF, RT, 20 h; [b] *t*-$BuMe_2SiCl$, Et_3N, DMF, RT, 18 h.

Scheme 50



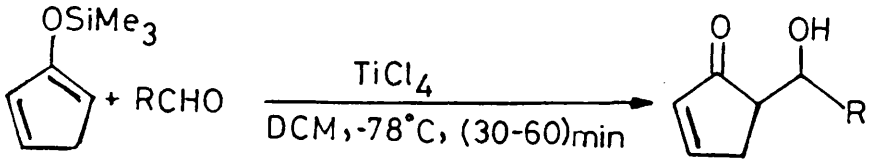
Scheme 51

give the cross-conjugated lithium dienolate (29), which equilibrates with the thermodynamically more stable fully conjugated lithium dienolate (31) before reacting with the silylating agent [pathway (b) in Scheme 51]. Similar equilibrations are known for cyclohex-2-enone dienolates and would explain why a greater proportion of the fully conjugated regioisomer was produced under thermodynamic conditions.[50]

All spectral data for silyl dienolates derived from (1) were in accord with their proposed structures (see Experimental and Section 2.3.1 for how the regiostructure of each isomer was determined).

2.4.2 Lewis acid-mediated aldol reactions of 2-(trimethylsiloxy)cyclopenta-1,3-diene

The Lewis acid-mediated reaction was initially attempted on 2-(trimethylsiloxy)cyclopenta-1,3-diene (41) (>90% single regioisomer) with titanium tetrachloride as the Lewis acid (Scheme 52). The results of this study are listed in Table 17.



(41) (30)

Scheme 52

Table 17

Diastereoselectivity in the $TiCl_4$-mediated aldol reaction of (41) with achiral aldehydes

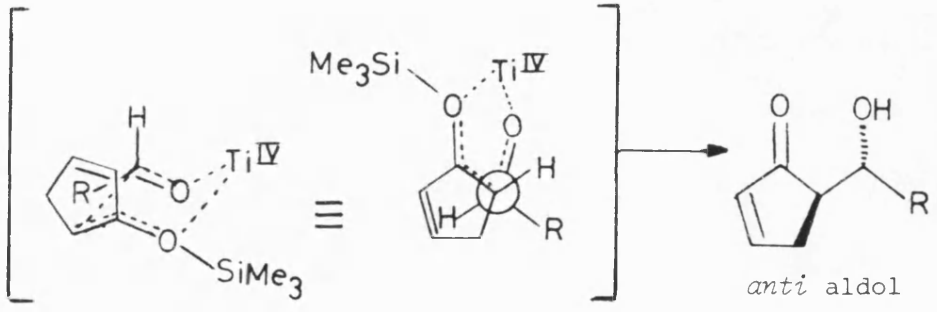
Aldehyde RCHO	Aldol product		
	Diastereoisomer ratio[a,b] *anti* : *syn*	Yield[c] (%)	Compound
EtCHO	86 : 14	46	(46)
Me_2CHCHO	>99 : 1	42	(49)
PhCHO	82 : 18	44	(35)
$PhCH_2CHO$	91 : 9	39	(36)

[a]Diastereoisomer ratio determined by g.l.c. [b]Relative stereochemistry and regiostructure determined by comparison with aldols prepared earlier. [c]Overall yield from (1) determined by g.l.c. analysis (internal standard).

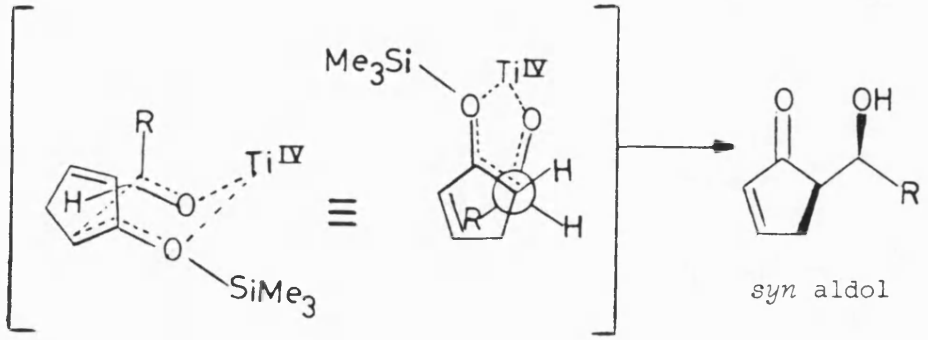
The 5-substituted cyclopent-2-enone aldols were produced in moderate yield. No 4-substituted cyclopent-2-enones (32), 2-substituted cyclopentenones (33) and (34) or dehydration products were isolated.

All the aldol additions showed good *anti* diastereoselectivity, the relative stereochemistry and regiostructure of the products was determined by comparing their spectral data with data of 5-substituted cyclopentenones prepared from LDA-mediated reactions of (1).

The *anti* diastereoselectivity observed in the $TiCl_4$-mediated reaction is consistent with a Mukaiyama-Chan[10b-c] chelated transition state, *exo* approach of the aldehyde and dienolate being favoured for steric reasons (Figure 19).



exo addition



endo addition

Figure 19

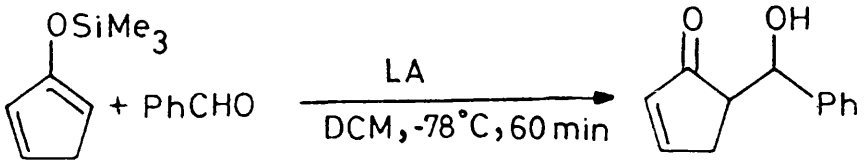
When $TiCl_4$-mediated aldol reactions were attempted on the less acid-labile 2-(*t*-butyldimethylsiloxy)cyclopenta-1,3-diene (43) (>90% single regioisomer), much smaller yields of the 5-substituted cyclopent-2-enone aldols were produced. The crude products contained mostly unreacted (43) and uncharacteristed polymeric material, which suggested longer reaction times and greater quantities of Lewis acid are necessary for efficient aldol reaction of (43).

When a $TiCl_4$-mediated aldol reaction was performed on *ca.* 65:35 mixture of siloxycyclopentadienes (41) and (42) with benzaldehyde, a complex multi-component mixture was obtained. Attempts to separate the components by chromatography (silica gel) resulted in the isolation of only small amounts of 5-substituted cyclopent-2-enone (35), benzaldehyde and uncharacterised resinous material. Although none of the aldol adducts which would be expected to be produced from a fully conjugated siloxycyclopentadiene was isolated, this does not rule out their formation, since the products could be lost or decomposed during the purification process or the amounts formed are too small to be detected by 60 MHz ^1H n.m.r. monitoring of the crude product.

Further research is necessary to examine methods of producing pure samples of the fully conjugated siloxycyclopentadiene (42) in good yield and then the results of Lewis acid-catalysed aldol reactions of this dienolate can be analysed with more confidence. For a successful aldol reaction involving a fully conjugated dienolate of (1), see section 2.6.

Having completed our study on the $TiCl_4$-mediated aldol reaction of cross-conjugated silyl dienolate (41), we turned out attention to other Lewis acids with a view to improving the yield and diastereoselectivity of the benzaldehyde-siloxycyclopentadiene reaction. The results of this study are shown in Scheme 53 and Table 18.

In general, good regioselectivity and good diastereoselectivity was observed; the *anti* diastereoisomer of (35) was produced in moderate yields. The diastereoselectivity was best in reactions in which the Lewis acid was able to chelate strongly with oxygens on the dienolate and aldehyde. The poor diastereoselectivity



(41) (35)

Scheme 53

Table 18

Diastereoselectivity in the aldol reaction of (41) with benzaldehyde mediated by different Lewis acids

Lewis acid LA	Aldol product Diastereoisomer ratio[a] *anti* : *syn*	Yield[b] (%)
$TiCl_4$	82: 18	44
$SnCl_4$	70 : 30	56
$AlCl_3$	82 : 18	63
BCl_3	83 : 17	27
TMS-OTf	49 : 51	35

[a] Diastereoisomer ratios determined by analysis.

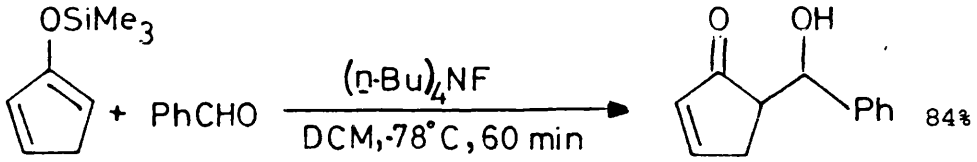
[b] Overall yield from (41) determined by g.l.c. analysis using an internal standard.

observed in the TMS-OTf-mediated reaction may have arisen as a result of the reaction proceeding *via* an alternative non-chelated transition state.

2.4.3 Fluoride ion-mediated aldol reactions of 2-(trimethylsiloxy)cyclopenta-1,3-diene

Literature reports have suggested that, under fluoride ion-mediated reaction conditions,[11] enolsilanes react with aldehydes to give mainly the *syn* diastereoisomers. Since we wished to have a

good method of forming *syn* diastereoisomers from cyclopent-2-enone (all aldol reactions so far discussed have been *anti* selective), we studied the aldol reaction between (41) and benzaldehyde in the presence of fluoride ion (Scheme 54).



(41) (35)

syn:*anti*

76:24

Scheme 54

The 5-substituted aldol (35) was produced in good yield. However, the diastereoselectivity of the reaction was the reverse of that observed in the Lewis acid-mediated reaction, the *syn* aldol being the major diastereoisomer. The reversal of diastereoselectivity may have resulted from the reaction proceeding *via* the open transition state shown in Figure 20. In fluoride ion-catalysed aldol reactions of (1), a "naked dienolate" (51) is formed and reacts with aldehydes *via* an open transition state in which the oxygens of the reactants are orientated as far apart as possible. Transition state (a) leading to the *syn* aldol is favoured over transition state (b) leading to the *anti* diastereoisomer, since there is a smaller non-bonded interaction between R and the cyclopentadiene ring.

Fluoride ion-mediated aldol reactions of (41) provide one method by which *syn* isomers of 5-substituted cyclopent-2-enone can be produced. Another method by which *syn* diastereoselectivity might be preferred is *via* a zirconium dienolate aldol reaction of (1).

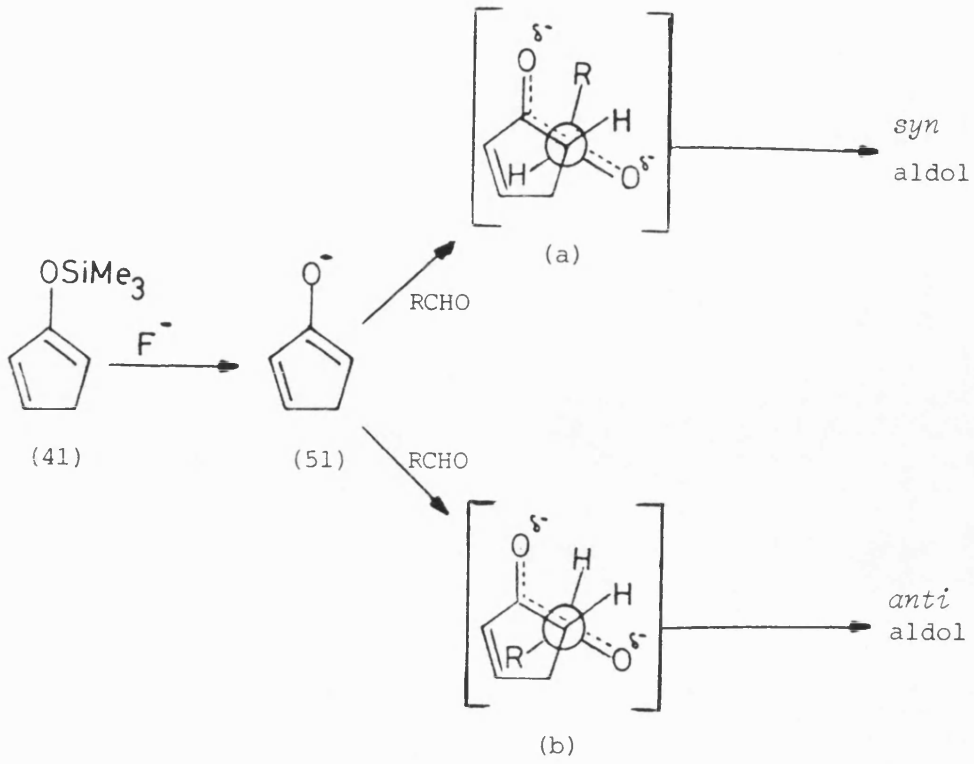


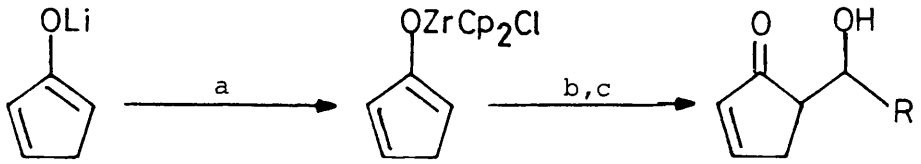
Figure 20

2.5 Aldol Reactions of the Zirconium Dienolate of Cyclopent-2-enone

Recent reports that aldol reactions involving zirconium enolates of cyclic ketones were *syn* selective prompted us to investigate the zirconium enolate reaction of (1).[17]

The zirconium dienolate of (1) was generated from its cross-conjugated lithium dienolate (29) by a transmetallation reaction and then reacted with benzaldehyde or hexanal under kinetic conditions (Scheme 55). The results of this brief study are listed in Table 19.

The *syn* aldol was the favoured diastereoisomer in both reactions. Diastereoselectivity was much better in the aldol reaction involving the bulkier benzaldehyde. The low yield of aldol product and large amount of unreacted aldehyde suggests that longer reaction times are necessary.



[a]$ZrCp_2Cl_2$, THF, -40 °C, 60 min; [b]RCHO, -78 °C, (60-80) min; [c]H_3O^+.

Scheme 55

Table 19

Diastereoselectivity in the aldol reaction of zirconium dienolate of (1) with benzaldehyde and hexanal

Aldehyde RCHO	Diastereomeric ratio *anti* : *syn*	Yield[a] (%) Aldol
PhCHO[b]	17 : 83	50 (35)
$Me(CH_2)_4CHO$[c]	47 : 53	30 (48)

[a]Yields corrected for recovered aldehyde

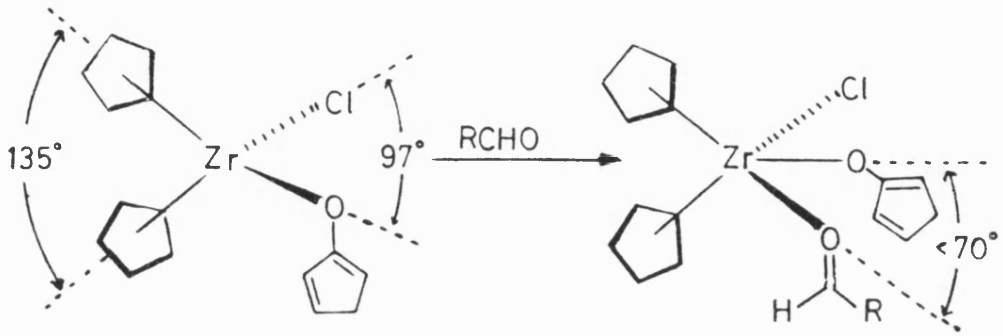
[b]Diastereoisomer ratio determined by comparison of the integrals of H-6 resonances in the ^1H n.m.r. spectrum.

[c]Diastereoisomer ratio determined by isolation of *syn* and *anti* aldols.

The reason for the *syn* diastereoselectivity is not clear, but it has been suggested that 16-electron zirconium dienolates such as (52) have a vacant ligation site that lies in the Cl-Zr-O plane.[17a] The Cl-Zr-O bond angle in zirconocenes similar to (52) are known to be 97°. When (52) is reacted with aldehydes an 18-electron aldehyde-enolate complex (53) is thought to be formed and this would have an even smaller O-Zr-O bond angle (<70°). The acute O-Zr-O

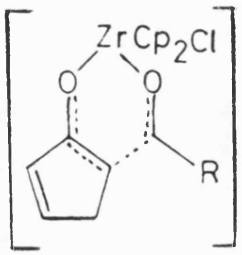
bond angle and the large size of the cyclopentadienyl ligands on the metal would severely distort the chelated transition states (54) which control the diastereoselectivity of the metal enolate aldol reaction (Figure 21).

The different levels of *syn* selectivity observed in the aldol reaction of (52) with benzaldehyde and hexanal may have resulted because there is a greater distortion in the transition state involving the bulkier benzaldehyde.



(52) (53)

16-electron zirconocene complex 18-electron zirconocene complex



(54)

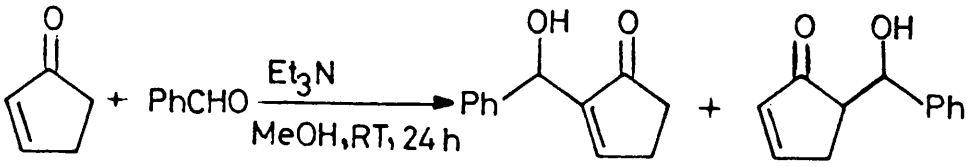
Figure 21

2.6 *Aldol Reactions of Cyclopent-2-enone under Thermodynamic Conditions

All the aldol reactions so far discussed have been performed under kinetic conditions. Enolisation under these conditions favours the formation of the cross-conjugated dienolate and this reacts with aldehydes to give exclusively 5-substituted cyclopent-2-enones.

During our investigation of the aldol chemistry of 2-(trimethylsiloxy)cyclopenta-1,3-diene (41) (Section 2.4.1), it was discovered that enolisation under thermodynamic conditions (Et_3N, DMF, $ClSiMe_3$, RT for 24 h) can result in mixtures containing large amounts (40%) of the fully conjugated silyl dienolate (42). It was of interest to us to see what effect these thermodynamic conditions would have on the regioselectivity and diastereoselectivity of the aldol reaction of (1).

Cyclopent-2-enone (1) was reacted with benzaldehyde in the presence of triethylamine as base. The result of this experiment is depicted in Scheme 56.



(1) (55) (35) *anti*:*syn*

25% 18% 47:53

yields refer to isolated regioisomer

Scheme 56

The aldol reaction showed no regioselectivity; a 58:42 mixture of the 2- and 5-substituted cyclopent-2-enones (55) and (35) was produced, the ratio of the two diastereoisomers of (35) being 47, *anti* to 53, *syn*. Thus no significant diastereoselectivity was achieved. The 5-substituted cyclopent-2-enone was identified by comparing its ^1H n.m.r. spectra with ^1H n.m.r. data reported earlier for aldol (35). The compound allocated the 2-substituted cyclopent-2-enone structure (55) had spectral data consistent with this structure. For example, mass spectrometric analysis (E.I.) revealed a M^+ at m/z 188, the ^{13}C n.m.r.

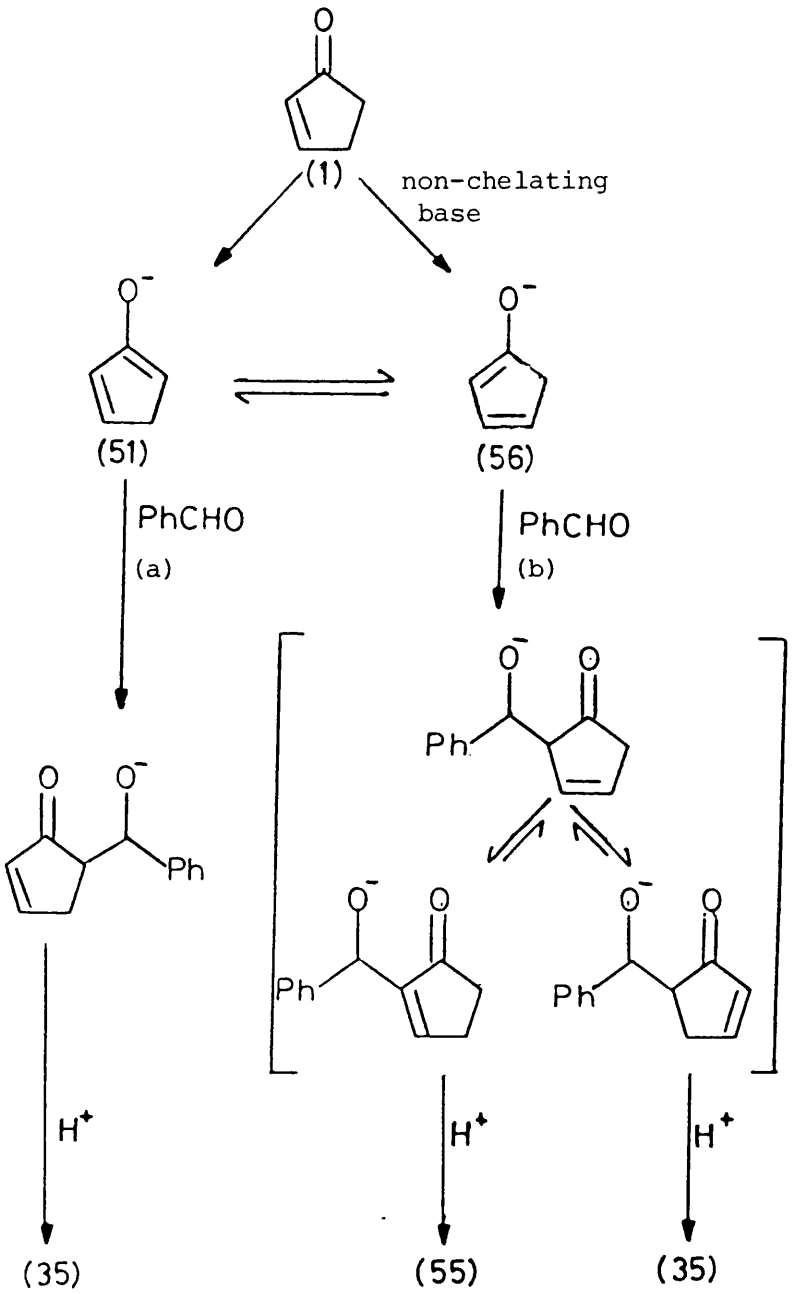
*Part of this work was performed in collaboration with Mr. Xiao-an Zhang.

spectra showed olefinic methine (C-3) at δ 159.6, olefinic quaternary carbon (C-2) at δ 147.8 and methylene carbons (C-5) and (C-4) at δ 35.2 and δ 26.6 respectively. The ^{1}H n.m.r. spectra contained a strong low field signal at δ (7.25-7.37), which integrates to six (phenyl ring and one olefinic proton) and carbinol resonance (H-6) was a singlet at δ 5.50.

Under the thermodynamic conditions depicted in Scheme 56, it is thought that enolisation results in the formation of an equilibrium mixture of the cross-conjugated and fully conjugated naked dienolates (51) and (56) respectively. [See preparation of siloxycyclopenta-1,3-dienes in Section 2.4.1 for support of this proposal.] The two regioisomers (55) and (35) may have been produced by the mechanism shown in Scheme 57. Some of the aldol (35) would be produced from the reaction of naked dienolate (51) with benzaldehyde [pathway (a)] and the rest of aldol (35) and aldol (55) would be produced from the aldol reaction between naked dienolate (56) and benzaldehyde [pathway (b)]. Initial addition taking place at C-2 of dienolate (56) gives the deconjugated aldolate, which would be unstable under equilibrating conditions and isomerise to the thermodynamically more stable aldolates which then react with a proton source to give aldols (55) and (35). No 4-substituted cyclopent-2-enones were produced in the addition reaction. This has literature precedent since the fully conjugated dienolate of cyclohex-2-enone normally favours reactions with electrophiles at C-2 to give 2-substituted cyclohex-3-enones.[49]

The aldol addition showed no diastereoselectivity when triethylamine was used as the base. No chelation is possible in the open transition states shown in Figure 22.

The *syn* diastereoisomer would be the major product if the reaction proceeds *via* an 'ideal open transition state',[14] since transition state (a) leading to the *syn* isomer is less crowded than transition state (b) leading to the *anti* isomer. The poor diastereoselectivity observed in the reaction under thermodynamic conditions probably occurs as a result of equilibration between



Scheme 57

the initially formed *syn* diastereoisomer and its thermodynamically more stable *anti* isomer.

Equilibration between *syn* and *anti* aldolates is consistent with an earlier study (Section 2.3.3), which suggested that there is very little energy difference between the favoured conformation of the *syn* and *anti* diastereoisomers.

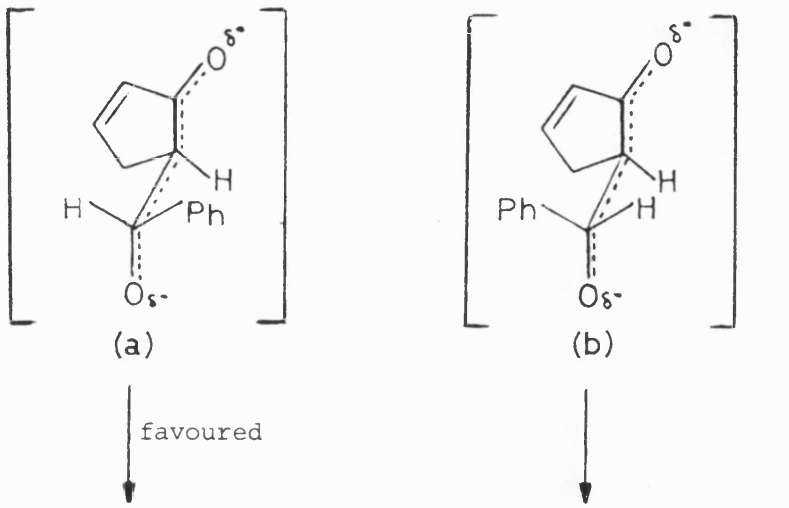


Figure 22

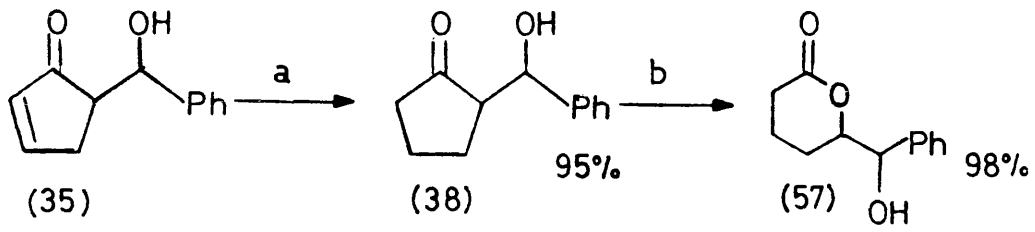
2.7 Synthetic Uses of 5-Substituted Cyclopent-2-enone Aldols

The aldol products derived from (1) should be useful intermediates in synthesis, since they have carbonyl and olefinic functional groups which could be used to build the polysubstituted cyclopentane units which are common in many natural products.[38]

Another structural unit which occurs widely in nature is the δ-lactone system. We have successfully prepared 5-substituted derivatives of both saturated and unsaturated δ-lactones by methods outlined in sections 2.7.1 and 2.7.2. respectively.

2.7.1 Preparation of 5-substituted saturated δ-lactones

When the 5-substituted cyclopent-2-enone (35) was catalytically reduced and the resultant 2-substituted cyclopentanone (38) subjected to a Baeyer-Villiger oxidation,[54] 5-(1'-hydroxy-1'-phenylmethyl)-pentan-5-olide (57) was obtained in good yield (Scheme 58).



[a]H_2, 10% Pd/C, EtOAc, RT, 2 h; [b]MCPBA, $NaHCO_3$, DCM, RT, 3 h.

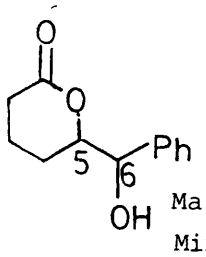
Scheme 58

The structure of the oxidation product (57) was determined from its spectral data. For example, the infrared showed a broad band at 3450 cm^{-1} (OH) and a strong absorption at 1710 cm^{-1} in the carbonyl region (CO saturated δ-lactone). Mass spectrometry (E.I.) gave a molecular ion at m/z 206, which is consistent with lactone (57), (molecular formula , $C_{12}H_{14}O_3$). The ^1H n.m.r. spectrum of the product showed a methine lactone-ether resonance (H-5) at δ 4.42* and six alicyclic protons at δ(1.50-2.55). The ^{13}C n.m.r. spectrum was even more revealing, the carbonyl resonance (C-1) at δ 171.3 is characteristic of a saturated δ-lactone [*cf* C-1 at δ 212* in aldol (35) and C-1 at δ 222.0* in aldol (38)]. The rest of the ^{13}C n.m.r. spectrum was consistent with structure (57), methine lactone-ether resonance (C-5) at δ 84.2* and three methylene resonances at δ 18.1* (C-3), 20.2* (C-4) and 29.6* (C-2).

The relative stereochemistry of lactone (57) was more difficult to determine. Baeyer-Villiger oxidations are known to proceed with retention of stereochemistry.[54] Since the major diastereoisomer of 5-substituted cyclopent-2-enone (35) had *anti* (5S, 1'S), (5R, 1'R) relative stereochemistry, it was anticipated that the major diastereoisomer of lactone (57) derived from it would also have (5S, 1'S), (5R, 1'R) stereochemistry, making it a *syn* diastereoisomer. This supposition was confirmed by comparing the $J_{5,6}$

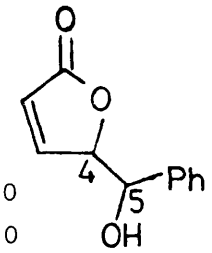
*Refers to average δ value for *syn* and *anti* aldols.

coupling constants of the major and minor diastereoisomer of (57) with the $J_{4,5}$ coupling constants of the *syn* and *anti* diastereoisomer of 5-(1'-hydroxy-1'-phenylmethyl)but-2-en-4-olide (103). [The relative stereochemistry of (103) was determined by comparison of its n.m.r. data with the n.m.r. data of compounds of known stereochemistry; see Section 3.3.1.]



(57)

$J_{5,6}$ (Hz)
Major isomer = 7.0
Minor isomer = 4.0



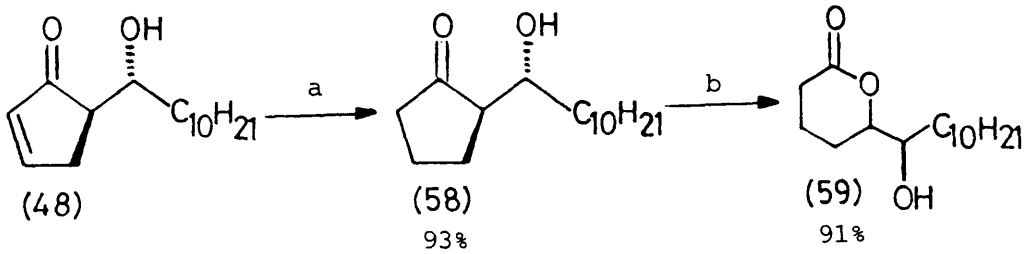
(103)

$J_{4,5}$ (Hz)
syn isomer = 7.0
anti isomer = 4.0

If it is assumed that the carbinol group and lactone-ether moiety have similar configurations in (57) and (103), then by comparing the vicinal coupling constants $J_{5,6}$ of (57) with $J_{4,5}$ of (103), it is clear that the major diastereoisomer of lactone (57) has *syn* relative stereochemistry.

Further support for the claim that the *anti* diastereoisomer of 2-substituted cyclopentanones are oxidised by MCPBA to the *syn* diastereoisomers of 5-substituted pentan-5-olides comes from a chemical correlation study.

When the *anti* diastereoisomer of aldol (48) was subjected to the reduction-oxidation sequence shown in Scheme 59, a single diastereoisomer (59) was obtained in good yield.



(48) → (58) 93% → (59) 91%

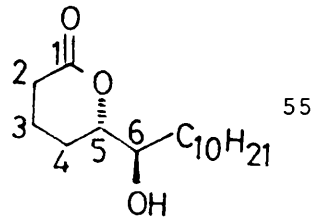
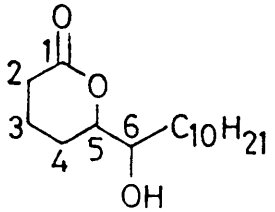
[a] H_2, 10% Pd/C, EtOAc, RT, 2.5 h; [b] MCPBA, $NaHCO_3$, DCM, RT, 3.5 h

Scheme 59

The spectral data of the oxidation product (59) was compared with the literature data for the *anti* diastereoisomer of 5-(1'-hydroxyundecyl)pentan-5-olide (60) (Table 20), which is an intermediate in Mori's[55] synthesis of the mosquito attractant phermone, *erythro*-(5S,1'R)-(+)—5—(1'-acetoxyundecyl)pentan-5-olide (Scheme 60).

Table 20

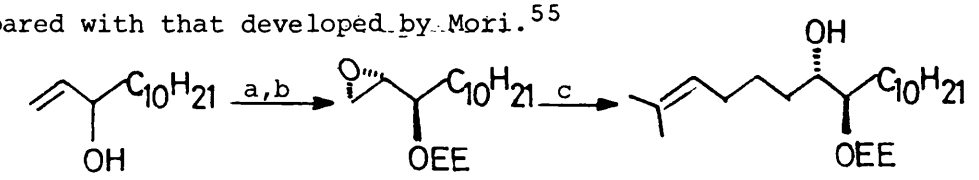
Melting points and selected spectral data for *anti*-(5S,1'R)-5-(1'-hydroxyundecyl)pentan-5-olide (60) and lactone (59)

Selected data	 lactone (60)	 lactone (59)
Melting point (°C)	67	52-55
I.r. (cm^{-1})	(KBr) 3440 (OH) 1715 (CO)	($CHCl_3$) 3580 (OH) 1720 (CO)
H-resonances δ_H (ppm) (J, Hz)		
H-5	4.25, dt (12.0, 18.0)	4.20, dt (10.0, 4.5)
H-6	3.82, m	3.57, dt (6.5, 4.5)
H-2a	2.57-2.66, m	2.62, bm (17.0)
H-2b	2.57-2.66, m	2.46, bm (17.0)
H-3a, 3b,	1.90-2.01, m	[1.66-2.02, bm
H-4a, 4b	1.73-1.90, m	

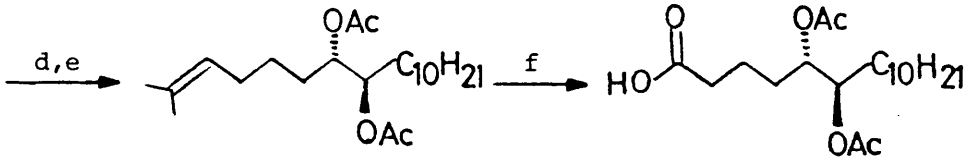
Inspection of Table 20 reveals lactones (59) and (60) have similar, but not identical, infrared and ^1H n.m.r. data. The melting points of (59) and (60) are very different. Close examination of the chemical shifts and splitting patterns of the carbinol resonance (H-6) and lactone-ether resonance (H-5) of (59) and (60) indicated that they had different stereochemistry at chiral atoms C-5 and C-6. Since lactone (60) is known to have *anti* relative stereochemistry, it is reasonable to assume that lactone (59)

has *syn* relative stereochemistry, which confirms our original suggestion that the *anti* diastereoisomer of the 2-substituted cyclopentanone is oxidised by MCPBA to the *syn* diastereoisomer of 5-substituted pentan-5-olide.

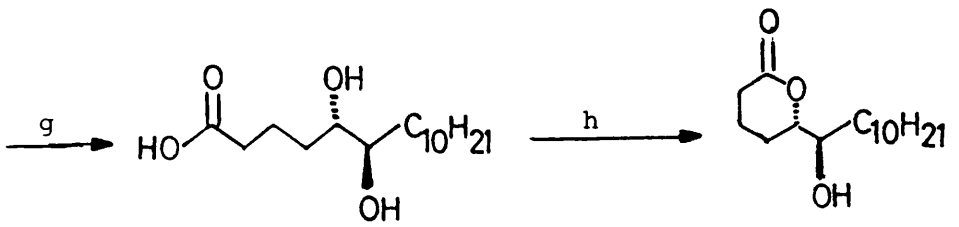
The sequence just described could be used to prepare a racemic mixture of the natural product *erythro* 5-(1'-acetoxy-undecyl)pentan-5-olide if it was performed on the *syn* diastereo-isomer of aldol (48). The *syn* diastereoisomer of (48) would be available in good yield from the fluoride ion mediated aldol reaction of silyl dienolate (41) and undecanal or *via* the aldol reaction of the zirconium dienolate of (1) with undecanal. This approach therefore represents a totally different synthetic stratagem for the synthesis of 5-(1'-hydroxyundecyl)pentan-5-olide, as compared with that developed by Mori.[55]



(±) (2S,3R) >91% ee

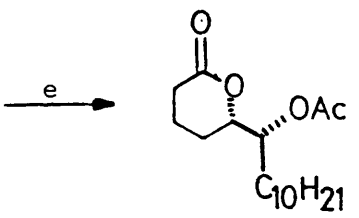


(7S,8R)



(5S,6R) (60)

(5S,6R) *anti* stereoisome



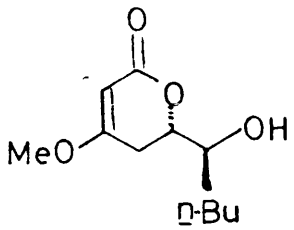
EE = ethoxy ethyl

[a] $Ti(i\text{-}PrO)_4$, *t*-BuOOH, di-isopropyl-D-(-)-tartrate, DCM; [b] $EtOCH{=}CH_2$, TsOH, ether; [c] $Me_2CH{=}CH(CH_2)_2MgBr$, CH_2Br_2, ether; [d] H_3O^+; [e] Ac_2O, pyridine, DMAP; [f] $NaIO_4$, $RuCl_3(H_2O)_n$, $MeCN\text{-}CCl_4$; [g] K_2CO_3 MeOH; [h] heat 160 °C.

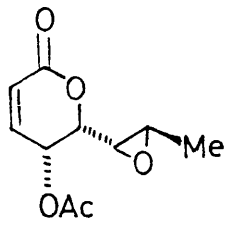
Scheme 60

2.7.2 Preparation of 5-substituted unsaturated δ-lactones

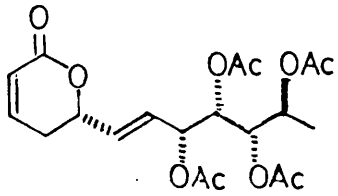
The 5-substituted unsaturated δ-lactone system is also a common structural unit in several natural products; for example pestalotin (61),[56] asperlin (62)[57] and anamarine (63).[58]



(61)



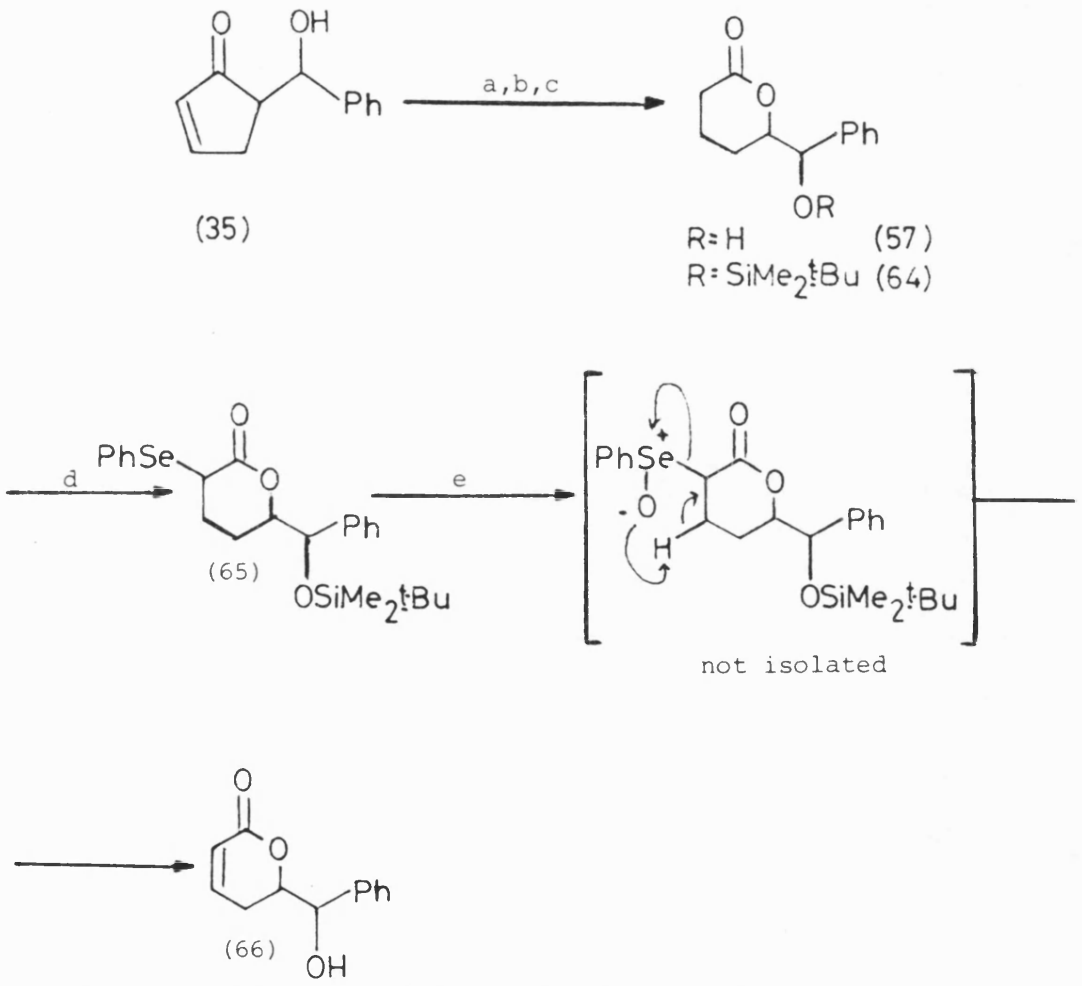
(62)



(63)

Initially, it was thought that the 5-substituted unsaturated δ-lactone system might be obtained by direct Baeyer-Villiger oxidation of a 5-substituted cyclopent-2-enone. There has been a report on Baeyer-Villiger oxidation of an α,β-unsaturated enone.[59] However, when the ring expansion reaction was attempted on aldol (35) using MCPBA as the oxidant, only starting reagents and uncharacterised resinous material was isolated. No δ-lactone or epoxide products could be detected by ^{1}H n.m.r. or i.r. monitoring of the crude reaction product. It was concluded from the above experiment that the conjugated carbon-carbon double bond was causing complications. It was decided, therefore, to try to prepare 5-substituted unsaturated δ-lactones by methodology, which would temporarily remove the carbon-carbon double bond and thus allow the Baeyer-Villiger reaction to take place. The carbon-carbon double bond would be re-introduced at a later stage. Two routes were followed which adopt this methodology, which are outlined in Schemes 61 and 62.

In the synthetic route depicted in Scheme 61, the 5-substituted pentan-5-olide (57) is first prepared by methodology discussed in Section 2.7.1 and then the lithium enolate of its silyl protected



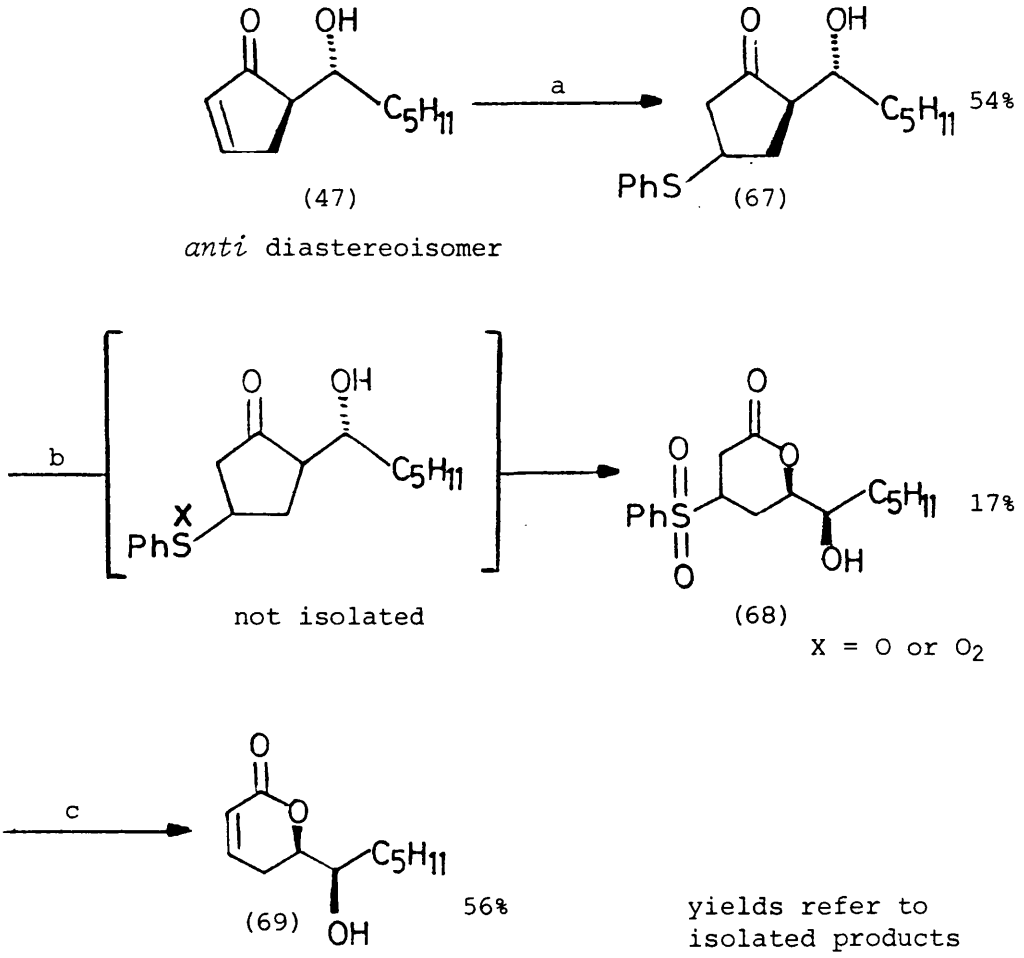
[a]H_2, 10% Pd/C, EtOAc, RT; [b]MCPBA, $NaHCO_3$, DCM, RT; [c]t-$BuMe_2SiCl$, imidazole, DMF; [e]LDA , THF, -78 °C, followed by PhSeBr or PhSeSePh at -78 °C; [e]$NaIO_4$, MeOH-H_2O or 30% H_2O_2-H_2O.

Scheme 61

alcohol (64) is reacted with a phenylselenyl halide in an effort to prepare the 2-phenylseleno-5-(1'-siloxyalkyl)pentan-5-olide (65). It is known that α-phenylselenocarbonyls similar to (65) are easily oxidised by hydrogen peroxide or sodium metaperiodate to alkyl-phenylselenoxides which are unstable and undergo *in situ syn* elimination to form α,β-unsaturated carbonyls.[60] Hence it should be possible to form the 5-substituted unsaturated δ-lactone (66) from (65).

When the synthetic route shown in Scheme 61 was attempted, the silyl-protected lactone (64) was prepared in good yield. [See Experimental Section for spectral data on (60).] However, attempts to convert it to the α-phenylselenolactone (65) using LDA and phenyl-selenyl chloride[60] or LDA and diphenyl diselenide[61] were unsuccessful. Only starting lactone (64), phenylselenyl residues and small amounts of uncharacterised material were detected by t.l.c. and ^{1}H n.m.r. analysis of the crude reaction product. Another attempt to prepare (66) from (64), in which the α-phenylselenocarbonyl (65) was not isolated but instead generated and reacted *in situ* with sodium metaperiodate also failed, a very complex inseparable multi-component mixture having resulted, which was not characterised. There is no obvious explanation for the lack of success of the phenyl-selenide addition. Self condensation or ring opening of the lactone did not appear to be a serious problem, since the major product from the addition reaction was unreacted lactone (64) which suggests the difficulty was either in the formation of the lithium enolate or that the reaction times employed were insufficient to produce enough lactone (61) to be detected by ^{1}H n.m.r. and t.l.c. analysis of the crude product.

In view of the lack of success in the preparation of (65) and the fact that the alternative route to 5-substituted unsaturated δ-lactones was proving to be more promising, we concentrated our efforts on the synthetic route shown in Scheme 62.



[a]PhSH, Et_3N, $CHCl_3$, 0 °C → RT, 2 h; [b]MCPBA, $NaHCO_3$, DCM, RT, 21 h; [c]DBU, $CHCl_3$, 20 h.

Scheme 62

The first step in the synthetic route depicted in Scheme 62 is a 1,4-nucleophilic addition reaction between thiophenol[62] and aldol (47). When this reaction was tried, 2-(hydroxyhexyl)-4-(phenylthio)cyclopentanone (67) was obtained in 54% yield. Cyclopentanone (67) had spectra data fully consistent with its proposed structure. For instance, the infrared spectrum showed strong absorptions at 3450 cm^{-1} (OH) and 1720 cm^{-1} (CO 2-substituted cyclopentanone) [*cf* 1680 cm^{-1}, CO unsaturated cyclopentanone]. The mass spectrometric analysis (E.I.) revealed major fragments at m/z 292 $(M)^{\ddagger}$, 274 $(M-H_2O)^{\ddagger}$ and 164 $(M-H_2O-PhSH)^{\ddagger}$. The ^1H n.m.r. spectrum showed no signal at δ 7.80 and δ 6.20, which indicated that the thiophenol had added across the C=C double bond of (47). Further support for a successful addition reaction was the strong broad signal at δ(7.18-7.50), which represents the five protons of the thiophenyl group, the broad multiplet at δ(2.00-2.80) being due to five alicyclic protons.

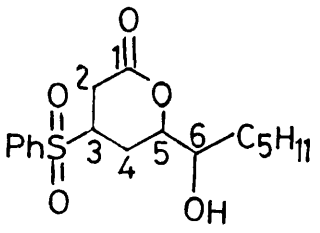
The thiophenol addition reaction created a new chiral centre in (67), hence four stereoisomers (two pairs of diastereoisomers) were possible, since the precursor of (67) had *anti* relative stereochemistry. ^{13}C and ^1H n.m.r. analyses of (67) indicated that it consisted of *ca.* 60:40 mixture of two pairs of diastereoisomers. Therefore the addition reaction shows a slight preference for one face of the cyclopent-2-enone ring in aldol (47).

When cyclopentanone (67) was subjected to Baeyer-Villiger oxidation conditions [3 equivalents of MCPBA, $NaHCO_3$ buffer, DCM, RT, 24 h), the major product isolated from the reaction mixture was identified as 3,5-disubstituted pentan-5-olide (68) (17% yield).

The structure of lactone (68) was determined from its spectral data. Mass spectrometric analysis (C.I.) revealed a very weak $(M+1)^{\ddagger}$ fragment at m/z 341 and stronger fragments at m/z 199 $(M+1-PhSO_2H)^{+}$ and 181 $(M+1-PhSO_2H-H_2O)^{+}$. The $(M+1)^{+}$ signal represents a molecular formula, $C_{17}H_{24}O_3S$, which proved the 'one-pot' oxidation had resulted in a ring expansion of the cyclopentanone unit and conversion of the phenyl sulphide substrate first to a phenyl sulphoxide and then to a phenyl sulphone. Further support for the treble oxidation sequence comes from the infrared spectrum, which showed strong absorptions at 1735 cm^{-1} (CO saturated δ-lactone) and 1305 cm^{-1} and 1150 cm^{-1}

($-SO_2-$) [*cf* sulphoxide-SO-stretches at 1070 and 1030 cm^{-1}].

The structure of lactone (68) was further elucidated from its ^{13}C and ^{1}H n.m.r. spectra. The ^{13}C spectra showed C-1 resonances at δ 167.6 and δ 168.9, which are characteristic of a carbonyl unit of a saturated lactone [compared with the δ 220.0 and δ 219.6 for the C-1 resonance of ketone (67)].



(68)

Table 21

Resonance	Chemical shift δ_H (ppm) and multiplicities (J, Hz)	
	major diastereoisomer	minor diastereoisomer
H-4	(2.00 - 2.44), m	
H-2	(2.60 - 2.93), m	
H-3	3.58, m	3.73, m
H-5	4.20, dt, (12.0, 3.5)	4.45, (9.5, 3.5)
H-6	3.58, m	3.58, m

Table 22

Resonance	Chemical shift δ_C (ppm)	
	major diastereoisomer	minor diastereoisomer
C-1	167.6	168.9
C-2	32.6	33.2
C-3	56.4	54.4
C-4	29.7	29.3
C-5	80.9	78.9
C-6	72.7	72.7

The C-5 resonances at δ 80.9 and δ 78.9 represent chiral methine carbons α to the lactone-ether moiety, which confirms the pentan-5-olide system is substituted at C-5. The rest of the ^{13}C and ^{1}H n.m.r. spectra were in agreement with lactone structure (68). (see Tables 21 and 22).

The diastereoisomer (two pairs of enantiomers) ratio of lactone (68) (*ca.* 60:40 from ^{1}H n.m.r. analysis) was almost identical to the diastereoisomer ratio of cyclopentanone (67) (*ca.* 60:40), which suggests that all of (67) is oxidised to (68). No intermediate oxidation products were isolated from the crude reaction product.

The final step in the synthetic route shown in Scheme 62 was the base-catalysed elimination of benzenesulphonic acid using DBU in chloroform.[63] Unfortunately, the reaction did not proceed to completion, even when an additional one equivalent of base was added and the mixture was heated at 40 °C for 2 h. The 5-substituted unsaturated δ-lactone product (68) was separated from unreacted starting material by chromatography. ^{13}C and ^{1}H n.m.r. analyses of (69) show it to be a single racemic diastereoisomer, which was assigned *syn* relative stereochemistry. This assignment was based upon previous findings (Section 2.7.1), which had suggested the *anti* diastereoisomer of cyclopentanones are oxidised by MCPBA to the *syn* diastereoisomer of pentan-5-olides. Since cyclopentanone (67) was known to have *anti* relative stereochemistry about the C^2-C^6 bond, it is assumed that lactones (68) and (69) have *syn* relative stereochemistry.

The 5-substituted unsaturated δ-lactone (69) had spectral data fully commensurate with its proposed structure. The infrared spectrum showed strong absorptions at 3570 (OH) and 1705 cm^{-1} (CO unsaturated ester). Mass spectral analysis (C.I.) revealed fragments at m/z 199 $(M+1)^+$, 181 $(M+1-H_2O)^+$ and 98 $[M+1-CH(OH)C_5H_{11}]^+$.

The ^{13}C n.m.r. spectrum was very informative, exhibiting a C-1 resonance at δ 163.8 and olefinic resonances C-2 and C-3 at δ 121.0 and δ 145.5 respectively.

The ^{1}H n.m.r. spectrum showed olefinic resonances H-2 and H-3 at δ 6.04 (ddd) and δ 6.95 (ddd) respectively. The splitting

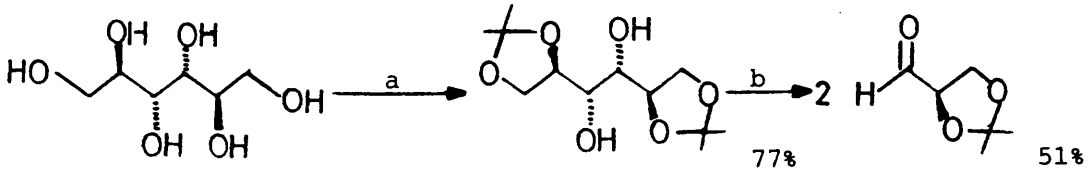
pattern and coupling constants of these resonances ($J_{2,3}$ = 10.0, $J_{3,4a}$ = 6.5, $J_{3,4b}$ = 3.0, $J_{2,4a}$ = 2.0 and $J_{2,4b}$ = 1.0 Hz) confirmed that the pent-2-en-5-olide is substituted at C-5.

The methodology just described provides an efficient and effective means of preparing 5-(hydroxyalkyl)pentan-5-olides and 5-(hydroxyalkyl)pent-2-en-5-olides; the relative stereochemistry of the products can be controlled to a fairly high degree. To make this methodology even more useful, we require a method of preparing 5-(hydroxyalkyl)cyclopent-2-enones and hence the saturated and unsaturated δ-lactones derived from them in optically pure form. With this goal in mind, the aldol reaction of (1) with a chiral aldehyde was investigated.

2.8 Aldol Reaction of Cyclopent-2-enone with a Chiral Aldehyde

In order to complete our investigation into the aldol chemistry of cyclopent-2-enone (1), it was necessary to study its reaction with a chiral aldehyde and thus to introduce the chiral dimension. The chiral aldehyde used for the study was (2R)-2,3-*O*-isopropylideneglyceraldehyde (70).[64] This molecule is extremely versatile, since it has both aldehyde and protected diol functionality and hence it has been used in several recent stereo-controlled natural product syntheses.[65]

Chiral aldehyde (70) was prepared in moderate yield from the cheap, readily available, D-mannitol (71), by the two-step protection-oxidation sequence shown in Scheme 63.[66]



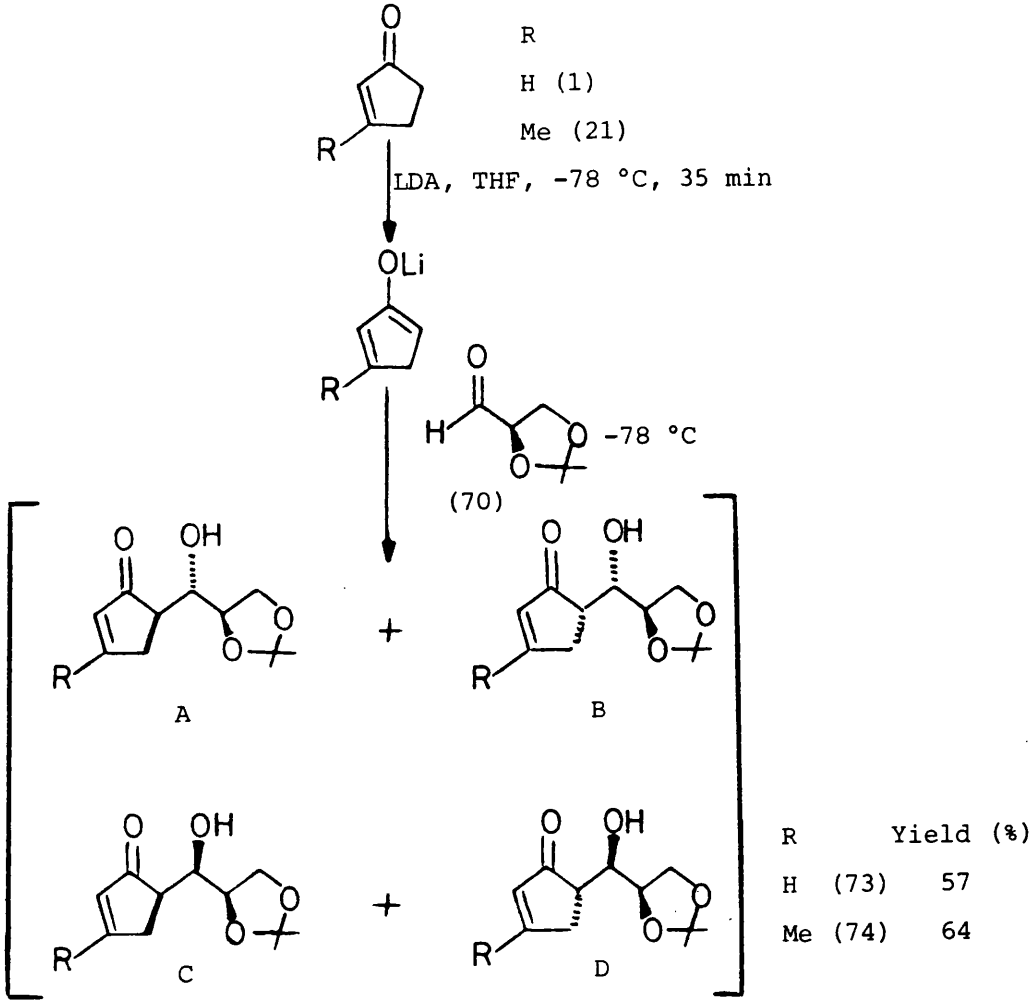
(71) (72) (70)

[a] $ZnCl_2$, MeCOMe, RT, 18 h; [b] $Pb(OAc)_4$, benzene, $NaHCO_3$, 1.5 h.

Scheme 63

Once (70) has been prepared, it is best used immediately, since it tends to polymerise on standing in air.[66a] However, it was possible to store (70) in a benzene matrix at -20 °C for several weeks without serious polymerisation, the aldehyde being redistilled before use.

When the aldehyde (70) was reacted with the cross-conjugated lithium dienolate of cylopent-2-enone (1) or 3-methylcyclopent-2-enone (21) under kinetic conditions, the 5-substituted cyclopent-2-enones (73) and (74) were obtained in 57% and 64% yields respectively (Scheme 64).



Scheme 64

The regiostructure of the 5-substituted cyclopent-2-enones (73) and (74) was determined by comparing their spectral data with spectral data of 5-substituted cyclopent-2-enones derived from aldol reactions of (1) with achiral aldehydes [*cf* Tables 23 and 24 with Tables 13 and 14 (section 2.3.2)].

Each of the aldols (73) and (74) has three chiral centres, one of which is fixed, its stereochemistry being the same as the starting aldehyde (70). The other two chiral centres are variable, their stereochemistry being determined by the level of asymmetric induction associated with the carbon-carbon bond forming reaction. Four diastereoisomers (A, B, C and D) are therefore possible for the two aldol reactions shown in Scheme 64. G.l.c. analysis of aldol products (73) and (74) indicate that they consist of mixtures of only two diastereoisomers in 58:42 ratio and 60:40 ratio respectively.

The absolute stereochemistry of the two diastereoisomers was difficult to determine from conventional spectroscopic techniques, but data listed in Tables 23 and 24 suggest the major and minor diastereoisomers of (73) and (74) have the same absolute stereochemistry.

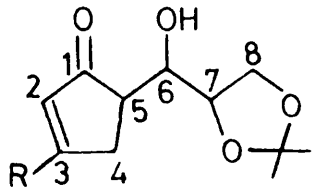
The ^1H n.m.r. spectra of aldols (73) and (74) were very similar (Table 23). The ^1H n.m.r. resonances of the chiral atoms often appeared as complex multiplets which overlapped with each other, even when the spectra were recorded at high field (400 MHz). It was extremely difficult accurately to assign chemical shifts to protons H-6, H-7, H-8a and H-8b and coupling constants $J_{5,6}$ and $J_{6,7}$ could not easily be estimated.

When the ^1H n.m.r. spectra of the major diastereoisomer of aldol (73) was recorded in C_6D_6, the chemical shifts of several of the protons changed, but the spectrum did not simplify sufficiently for the vicinal coupling constants $J_{5,6}$ and $J_{6,7}$ to be determined (Table 25). A homonuclear spin decoupling experiment was performed on the major diastereoisomer of aldol (73) and this provided some information on coupling constants $J_{5,6}$ and $J_{6,7}$.

When the ^1H n.m.r. spectrum was taken with irradiation at H-5 (δ 2.51), the signal due to the H-6 resonance (carbinol proton) simplified from a broad triplet (*ca.* J = 7.5 Hz) to a doublet (*ca.* J = 7.0 Hz), which indicated vicinal coupling constants $J_{5,6}$ and $J_{6,7}$ were both *ca.* 7.0-7.5 Hz. The methylene ring protons also

Table 23

^{1}H N.m.r. data on cyclopent-2-enone aldols (73) and (74)



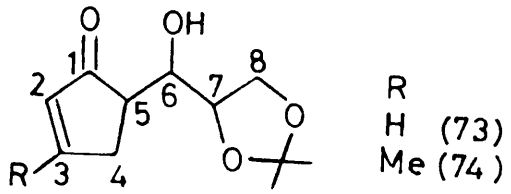
R
H (73)
Me (74)

Resonance	Chemical shifts δ_H (ppm) and multiplicities (J, Hz)			
	Aldol (73)		Aldol (74)	
	Major diastereoisomer	Minor diastereoisomer	Major diastereoisomer	Minor diastereoisomer
H-2	6.22, dt (6.0, 2.0)	6.21, dt (6.0, 2.0)	5.96, s[a]	5.93, s[a]
H-3	7.80, dt (6.0, 2.5)	7.82, dt (6.0, 2.5)	-	-
H-4a	2.76, dq (18.0, 2.5)	2.75, ddt (18.0, 6.0, 2.5)	2.66, m (18.0)	2.61, dm (18.0)
H-4b	2.91, ddt (18.0, 6.0, 2.5)	2.88, dq (18.0, 2.5)	2.77, dd (18.0, 6.0)	(2.72-2.82), m
H-5	2.51, ddd (7.5, 6.0, 2.5)	2.70, m	2.55, m	
H-6	3.66, bt (7.5)	4.00,[b] dd (8.5, 5.0)	3.66, bt (7.5)	(3.94-4.18), m
H-7	4.03, m	4.05,[b] m	(3.90-4.17), m	
H-8a, 8b	4.12, bm	4.14, m		

[a]Additional fine coupling. [b]Assignment may be interchanged.

Table 24

^{13}C N.m.r. chemical shifts in cyclopent-2-enone aldols (73) and (74)



R
H (73)
Me (74)

Chemical shifts δ_C (ppm)																
Group	Major diastereoisomer								Minor diastereoisomer							
R	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8
Me	212.6	129.6	180.4	36.9	49.5	73.8	78.7	67.2	211.0	130.2	180.1	33.8	49.6	70.5	76.8	67.0
H	212.9	133.5	165.9	33.0	47.8	73.6	78.3	67.1	211.7	134.0	166.0	29.6	47.8	70.6	76.7	66.9

Table 25

Comparison of ^1H n.m.r. data of the major diastereoisomer of (73) recorded in $CDCl_3$ and C_6D_6

Chemical shifts δ_H (ppm) and multiplicities (Hz)		
Resonance	$CDCl_3$ (400 MHz)	C_6D_6 (270 MHz)
H-2	6.22, dt (6.0, 2.0)	5.78, dt (6.0, 2.0)
H-3	7.80, dt (6.0, 2.5)	6.81, dt (6.0, 2.5)
H-4a	2.76, dq (18.0, 2.5)	2.34, dq (18.0, 2.5)
H-4b	2.91, ddt (18.0, 6.0, 2.5)	2.25, bm (18.0)
H-5	2.51, ddd (7.5, 6.0, 2.5)	2.13, m
H-6	3.66, bt (7.5)	3.46, bt (7.5)
H-7	4.03, m	(4.00-4.13), bm
H-8a, 8b	4.12, bm	

simplified from a doublet of quartets (J = 18.0, 2.5 Hz, H-4a) and a doublet of doublets of triplets (J = 18.0, 6.0, 2.5 Hz, H-4b) to two broad doublets (J = 18.0 Hz) which showed some fine coupling (< 2.0 Hz). The rest of the ^1H n.m.r. spectrum was unaffected.

When the coupling constant $J_{5,6}$ for the major diastereoisomer of aldol (73) (~7.5 Hz) was compared with the $J_{5,6}$ coupling constants for the *syn* (~3.0 Hz) and *anti* (~9.5 Hz) diastereoisomers of 5-substituted cyclopent-2-enones derived from achiral aldehydes (Table 14 in section 2.3.2), it seemed likely that the major diastereoisomer of (73) has *anti* relative stereochemistry about the C_5-C_6 bond, since its coupling constant $J_{5,6}$ is closer to the $J_{5,6}$ coupling constant of an *anti* diastereoisomer than a *syn* diastereoisomer. The $J_{6,7}$ coupling constants were less useful in determining the relative stereochemisty about C_6-C_7 bond, since the favoured conformation of aldol (73) about the C_6-C_7 bond was not known.

Further support for the suggestion that the major diastereoisomer of aldol (73) has *anti* relative stereochemistry about the C_5-C_6 bond comes from a comparison of its ^{13}C n.m.r. data (Table 23) and ^1H n.m.r. data (Table 24) with n.m.r. data for 5-substituted cyclopent-2-enones derived from achiral aldehydes (Tables 13 and 14).

It was noted in Section 2.3.2 that the C-4 and C-6 resonances of *anti* cyclopent-2-enone aldols have chemical shift values *ca.* 2-4 ppm higher than their corresponding *syn* diastereoisomers. Applying this criterion to the major and minor diastereoisomers of (73) would suggest that the major diastereoisomer has *anti* relative stereochemistry about the C_5-C_6 bond (see Table 23). (This assignment assumes that the major and minor diastereoisomers of aldol differ only in their steroechemistry about the C_5-C_6 bond.)

It was also noted that the H-6 resonance of *syn* aldols usually appears at chemical shifts *ca.* 4.1-4.5 ppm and H-6 resonance for *anti* aldols at chemical shifts *ca.* 3.4-3.9 ppm, which would again indicate that the major diastereoisomer of (73) has *anti* relative stereochemistry about the C_5-C_6 bond, since H-6 resonance is at δ 3.66, but the minor diastereoisomer would have either *syn* or *anti* stereochemistry about the C_5-C_6 bond, since its H-6 resonance occurs at δ 4.00.

The above suggestions, although interesting, are only speculative. For a more convincing argument on assignment of stereochemistry based on coupling constants and trends within the n.m.r. spectra, we require spectral data on all four diastereoisomers of aldol (73).

Although we are not yet able unequivocally to assign absolute stereochemistry to the major and minor diastereoisomers of aldols (73) and (74), literature reports on organolithiate additions to aldehyde (70) in conjunction with our earlier findings on the diastereoselectivity associated with aldol reactions of (1) and achiral aldehydes allows us to theorise on the stereostructure of the major and minor diastereoisomers of (73) and (74).

It was reported in Section 2.3.2 that (1) undergoes aldol reactions with achiral aldehydes to furnish predominantly *anti* aldols and the diastereoselectivity of this reaction increases with the steric bulk of the aldehyde. Since the chiral aldehyde (70) is of a similar size as 2—methylpropanal, an aldol reaction involving (70) and (1) would be expected to exhibit good simple diastereoselectivity. Hence the major diastereoisomer of (73) should have stereostructures A or D in Scheme 64.

Literature reports on nucleophilic addition reactions between organolithiates and chiral aldehyde (70) indicate that it shows

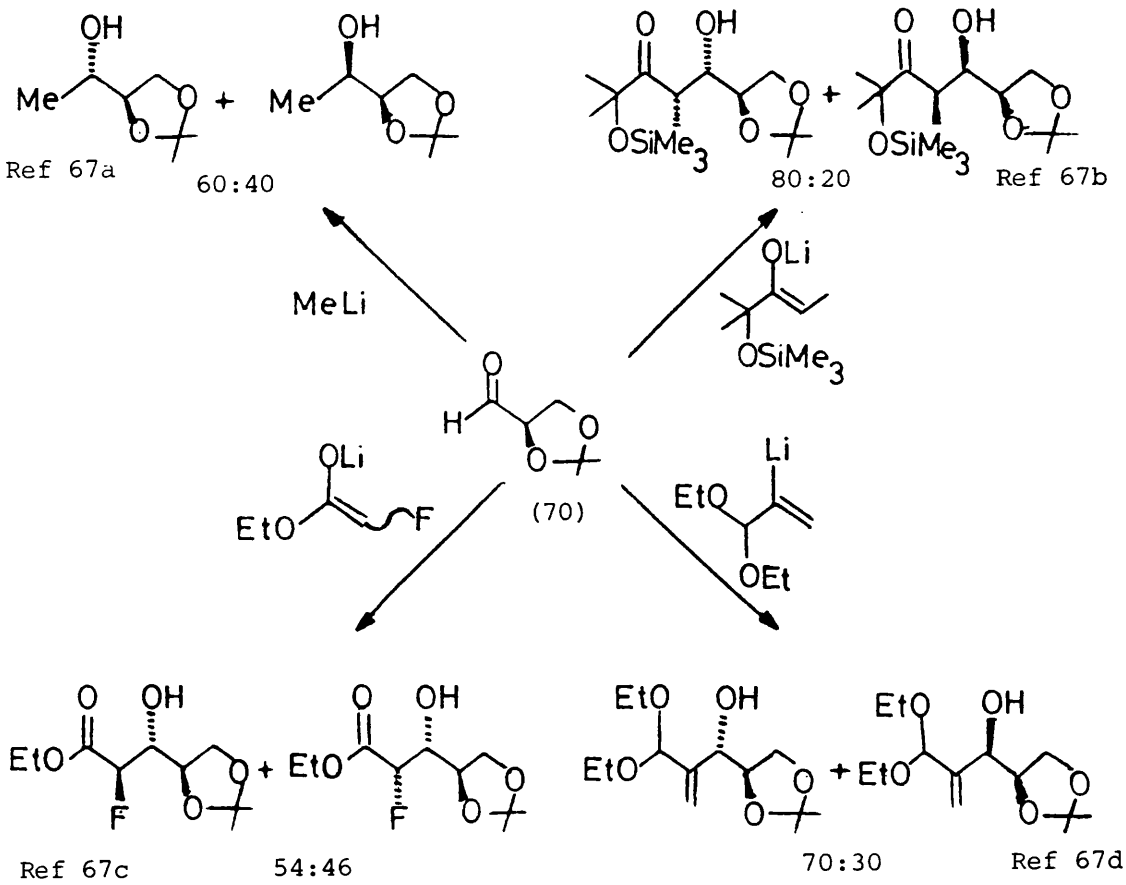
moderate inherent diastereofacial preference;[64] the stereochemistry of the major product is normally that predicted by the Felkin-Anh[24] model for α-asymmetric induction, since there is usually no chelation between the lithium counterion and the oxygen atoms of the isopropylidene group (see Figure 11 in Section 1.4.1). Examples of the variable level of diastereofacial selectivity normally observed in nucleophilic additions between aldehyde (70) and organolithiates are shown in Scheme 65.[67a-d]

Applying the Felkin-Anh model for α-asymmetric induction to the aldol reactions between aldehyde (70) and enones (1) and (29) (Scheme 64) suggests the favoured diastereoisomers of aldol (73) and (74) would have *anti* relative stereochemistry about the C_6-C_7 bond, *i.e.*, stereostructures A and B.

When our results on simple diastereoselectivity are combined with literature reports on diastereofacial selectivity of aldehyde (73) theory predicts the major diastereoisomer of aldols (73) and (74) should have structure A in Scheme 64 [*anti* stereochemistry about C_5-C_6 bond and *anti* stereochemistry about the C_6-C_7 bond, (5R, 6S, 7R)]. The stereochemistry of the minor isomers of (73) and (74) cannot be predicted with the same confidence. If the aldol addition shows good diastereofacial selectivity and poor simple diastereoselectivity, then the minor aldol products will have stereostructure B. If the aldol reactions show good simple diastereoselectivity and poor diastereofacial selectivity, then the minor aldol products will have stereostructure D.

At the time of writing this thesis, insufficient data are available to confirm or disprove the above suggestions, but research currently in progress within this laboratory is concentrating on methods of determining the absolute stereochemistry of the major and minor diastereoisomers of (73) and (74). These methods include the following:

(i) *X*-Ray structure analysis of crystalline compounds derived from single diastereoisomers of (73) and (74).

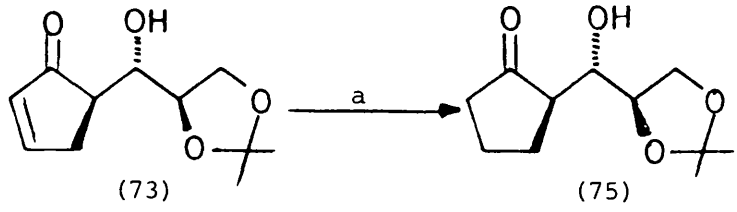


Scheme 65[67a-d]

Diastereofacial selectivity in the nucleophilic addition reaction between organolithiates and (70)

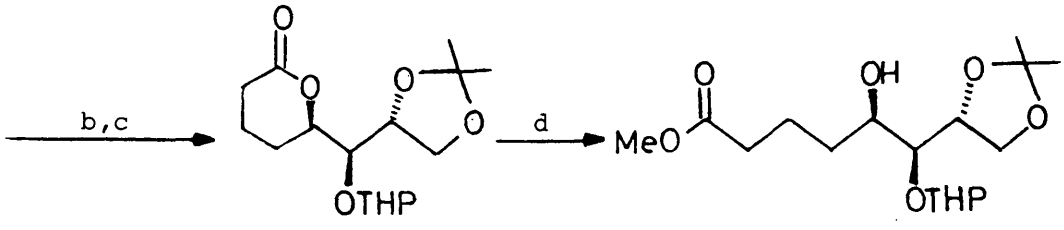
(ii) Chemical correlation of compounds derived from (73) with compounds of known absolute stereochemistry. For example, the major diastereoisomer of aldol (73); we assume it to have stereostructure A, which can be converted to the 5-substituted pentan-5-olide (76) by the methodology described in Section 2.7.1. If lactone (76) is then ring opened by base, the tetrahydroxycarboxylic ester (77) would be produced (Scheme 66).

Tetrahydroxycarboxylic ester (77) is an intermediate in Corey's[68] synthesis of 6-*epi*-leukatriene C (LTC) (Scheme 67). Comparison of the spectral data from the product (77) prepared from the major diastereoisomer of aldol (73) with published spectral data on the Corey intermediate would confirm or disprove our suggestion that the major diastereoisomer of (73) has stereostructure A.



(73) (75)

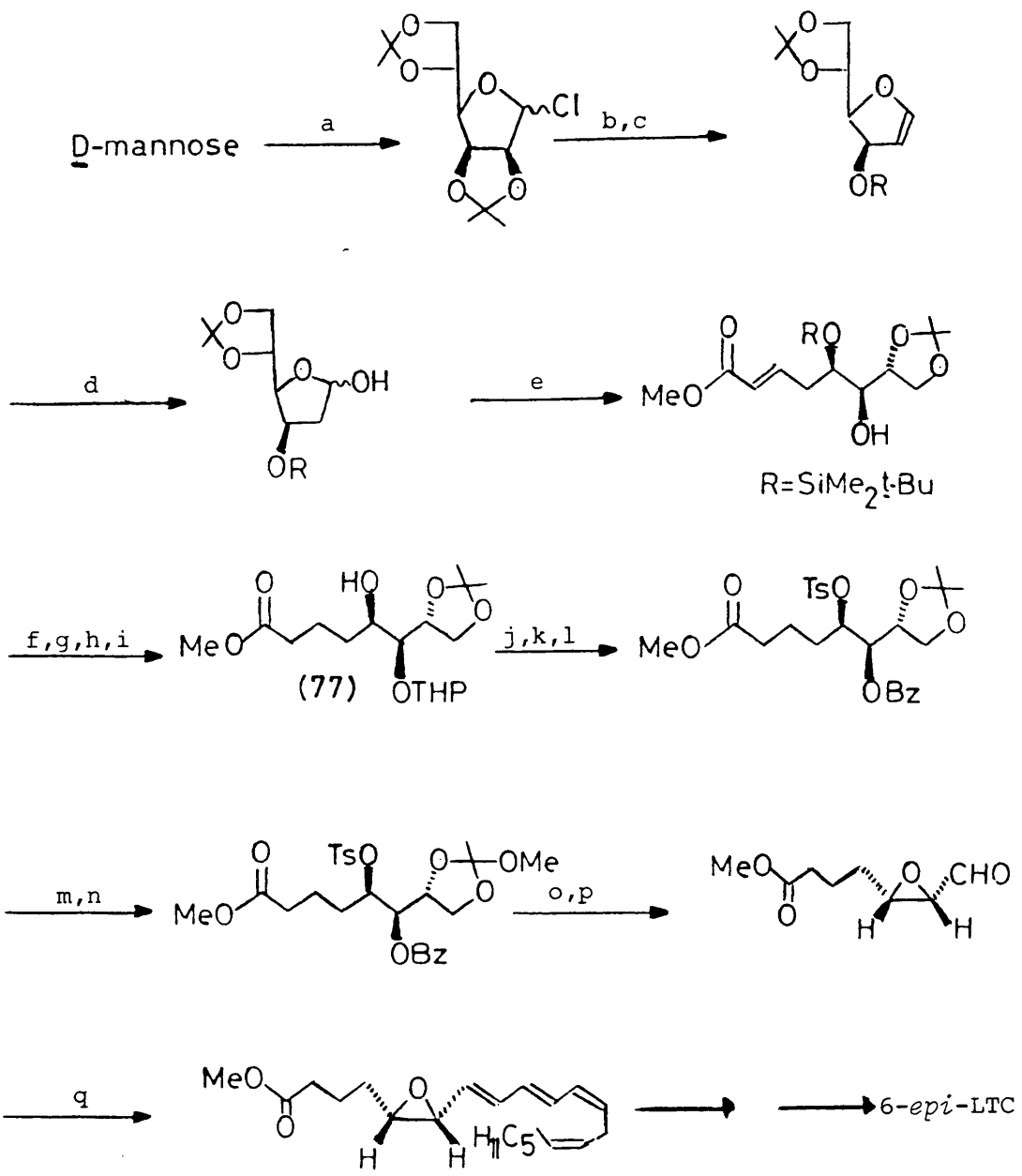
diastereoisomer A



(76) (77)

[a]H_2, 10% Pd/C, EtOAc; [b]MCPBA, $NaHCO_3$, DCM; [c]dihydropyran, TsOH, DCM; [d]MeOH, Et_3N.

Scheme 66



[a]acetone, H^+, then Ph_3P, CCl_4; [b]Na, liq. NH_3; [c]*t*-$BuMe_2SiCl$, DMF, imidazole; [d]$Hg(OAc)_2$, THF-H_2O, 0 °C then NaI and $NaBH_4$, -10 °C; [e]$Ph_3P{=}CHCO_2Me$, THF, benzoic acid, 70 °C; [f]H_2, Pt/C; [g]dihydropyran, TsOH, DCM; [h]$(n\text{-}Bu)_4NF$, THF; [i]MeOH, Et_3N; [j]TsCl, pyridine; [k]PPTS, MeOH; [l]BzCl, pyridine; [m]HCl, MeOH; [n]$MeC(OMe)_3$, DCM, TsOH; [o]K_2CO_3, MeOH; [p]$Pb(OAc)_4$, DCM, $NaHCO_3$ -45 °C; [q]Wittig reaction.

Scheme 67

CHAPTER 3

Regio- and Diastereo-Selectivity in the Directed Aldol Reactions of But-2-en-4-olide

Although some of the uses of α,β-unsaturated and β,γ-unsaturated but-2-en-4-olides as efficient synthetic units are well documented,[69] there has been no systematic investigation of the aldol chemistry of the but-2-en-4-olide system. To fill this gap in the literature, a complementary and parallel study to that described in Chapter 2 was undertaken.

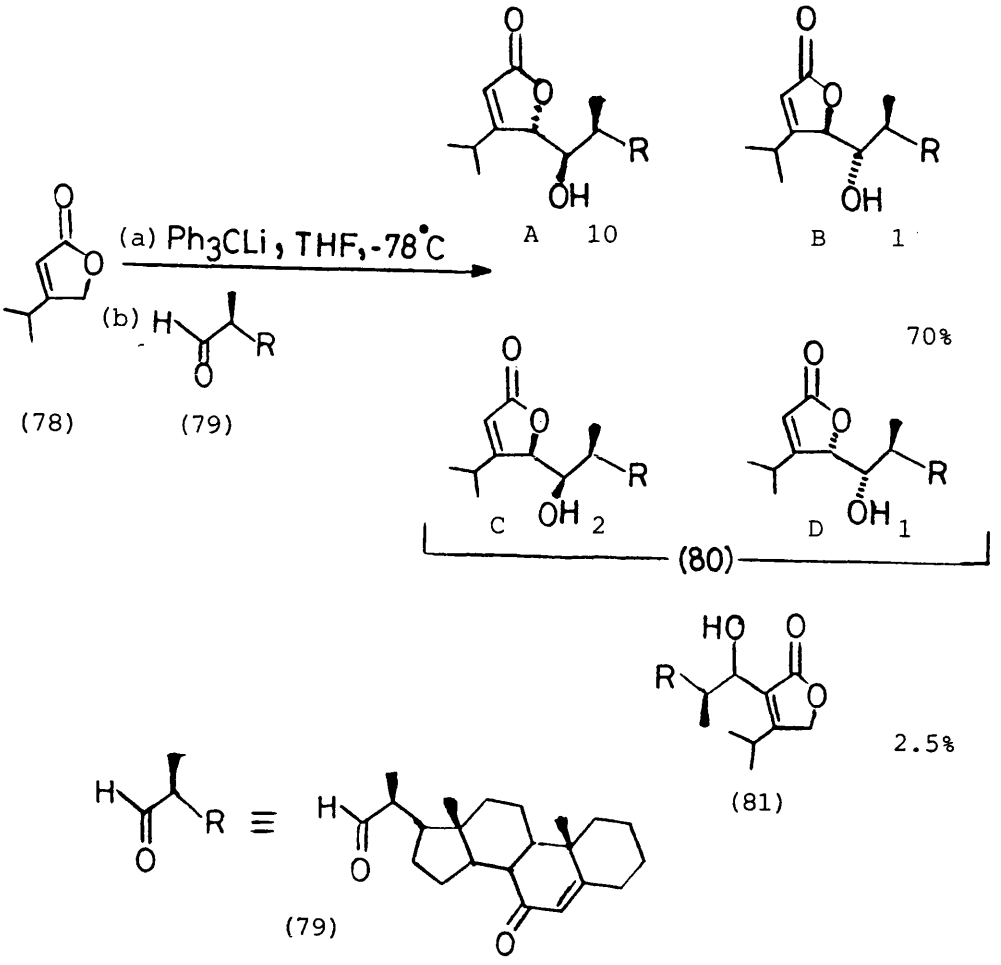
3.1 Review of the Aldol Chemistry of But-2-en-4-olide and its silyl dienolate [2-(Trialkylsiloxy)furan]

Before discussing the results of our investigation of the aldol chemistry of the silyl dienolate and lithium dienolate of but-2-en-4-olide (2), a brief summary of published aldol reactions of both dienolates is described.

3.1.1 Aldol reactions of but-2-en-4-olides under basic conditions

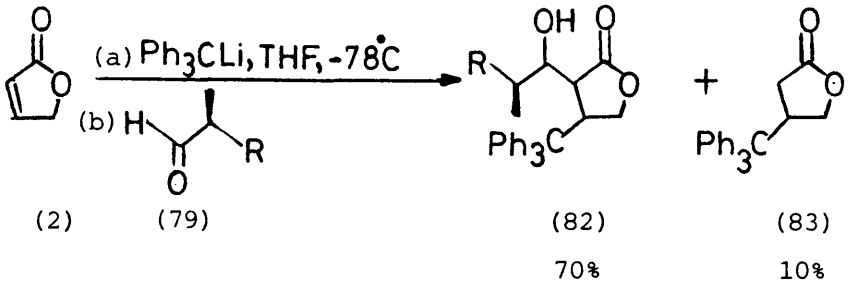
The relatively small number of reports which have appeared suggests that aldol reactions of (2) under base-mediated conditions are problematic. The only successful aldol reactions have been with 3-alkyl or 3-alkoxy substituents.

The first successful report on a base-mediated aldol reaction of a but-2-en-4-olide was made by McMorris and co-workers.[70] They investigated the aldol reaction of 3-isopropylbut-2-en-4-olide (78) with the chiral aldehyde (79), (Scheme 68). The reaction showed good regioselectivity with the 4-substituted but-2-en-4-olide (80) (mixture of four diastereoisomers A, B, C and D) being formed in 70% yield. Only a very small amount (2.5%) of the 2-substituted aldol (81) was detected. The reaction showed moderate simple diastereoselectivity (*anti*:*syn* ratio = 11:3) and good diastereofacial selectivity. The major diastereoisomer (A in scheme 69) was that predicted by the Felkin-Anh model for α-asymmetric induction.[24]



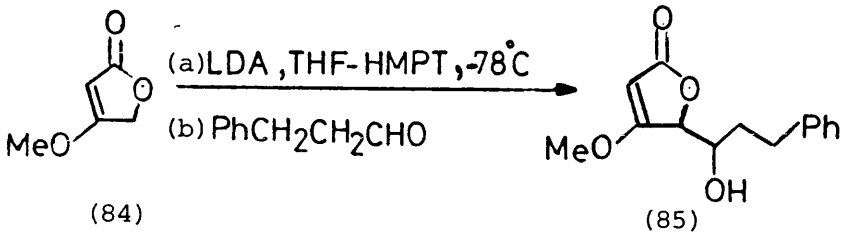
Scheme 68

When a similar aldol reaction was attempted with the parent but-2-en-4-olide (2), none of the expected 4-substituted but-2-en-4-olide was obtained. Instead, the trityl anion acted as a nucleophile producing a 1,4-nucleophilic addition reaction to (2), to give butan-4-olides (82) and (83) (Scheme 69).



Scheme 69

Another report on the base-mediated aldol reactions of 3-substituted but-2-en-4-olide has been made by Pelter and co-workers.[71] The lithium dienolate of 3-methoxybut-2-en-4-olide (84) reacts with 3-phenylpropanal to give a diastereomeric mixture of the 4-substituted but-2-en-4-olide (85) (Scheme 70).

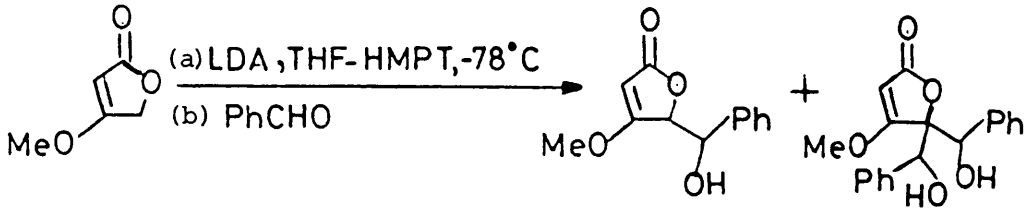


(84) (85)

ca. 1:1 mixture of diastereoisomers

Scheme 70

A similar reaction with benzaldehyde as the electrophile was less regioselective and a 1:1 mixture of mono- and di-substituted but-2-en-4-olides (86) and (87) was formed[71] (Scheme 71). No information on the yields or the relative stereochemistry of the aldol products was provided.



(84) (86) (87)

ca. 1:1 mixture

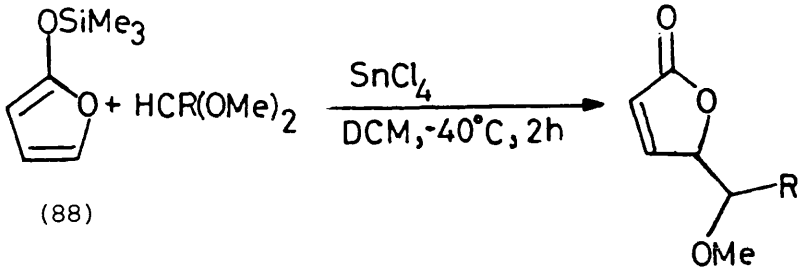
Scheme 71

In general most base-mediated aldol reactions of but-2-en-4-olides have been reported to give poor regioselectivity, multi-component mixtures often being produced. Better regioselectivity and diastereoselectivity have been achieved in aldol reactions involving the silyl dienolates of but-2-en-4-olides, *i.e.*, 2-(trialkylsiloxy)furans.

3.1.2 Aldol reactions of 2-(trimethylsiloxy)furans mediated by Lewis acids

Much of the early work on the aldol reaction of 2-(trimethylsiloxy)furan (88) was performed by Takei and co-workers.[72]

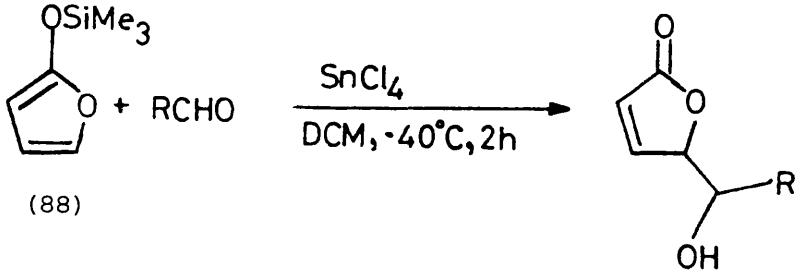
In the presence of stannic chloride, (88) was shown to undergo aldol reactions with acetals and aldehydes to give 4-substituted but-2-en-4-olides (Schemes 72 and 73 respectively).



(88)

R	Yield (%)
Ph	77
$PhCH_2CH_2$	92

Scheme 72



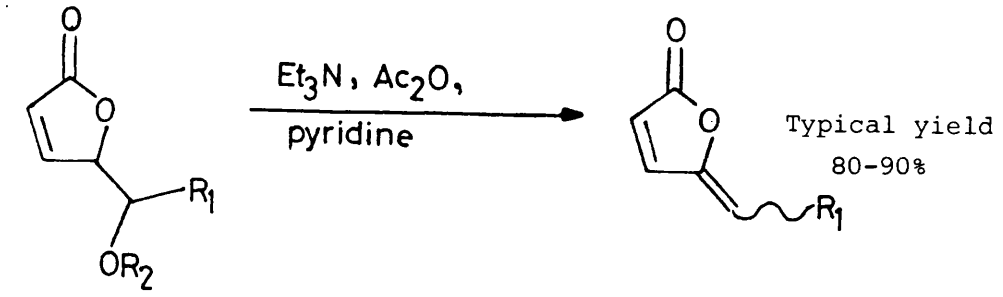
(88)

R	Yield (%)
Ph	95
$PhCH_2CH_2$	90

Scheme 73

No discussion on the relative stereochemistry of the aldol products was given, but dehydration of the products resulted in mixtures of *cis*- and *trans*-isomers of 4-alkylidene but-2-en-4-olides (Scheme 74).

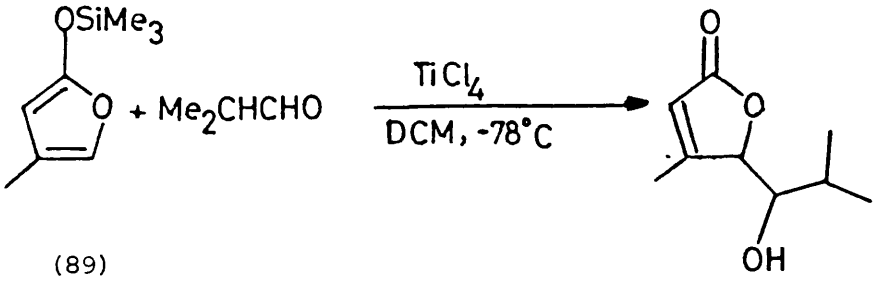
A titanium tetrachloride-mediated aldol reaction of 4-methyl-2-(trimethylsiloxy)furan (89) and 2-methylpropanal has been reported to give a diastereomeric mixture of the 4-substituted but-2-en-4-olide[73] (90) (Scheme 75). It was suggested that the *syn* diastereoisomer was the major aldol, but no explanation was given for the diastereoselectivity observed in the reaction.



R_1 = aryl or alkyl; R_2 = H or Me

Mixture of *cis* and *trans* isomers

Scheme 74



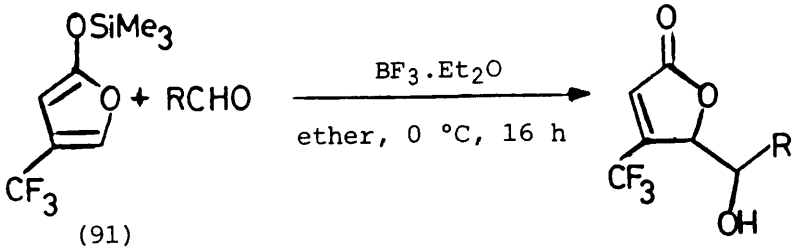
(89)

(90)

4:1 mixture of diastereoisomers

Scheme 75

A group of Japanese workers[74] have recently studied the $BF_3.Et_2O$-mediated aldol reactions of 4-(trifluoromethyl)-2-(trimethylsiloxy)furan (91), (Scheme 76).

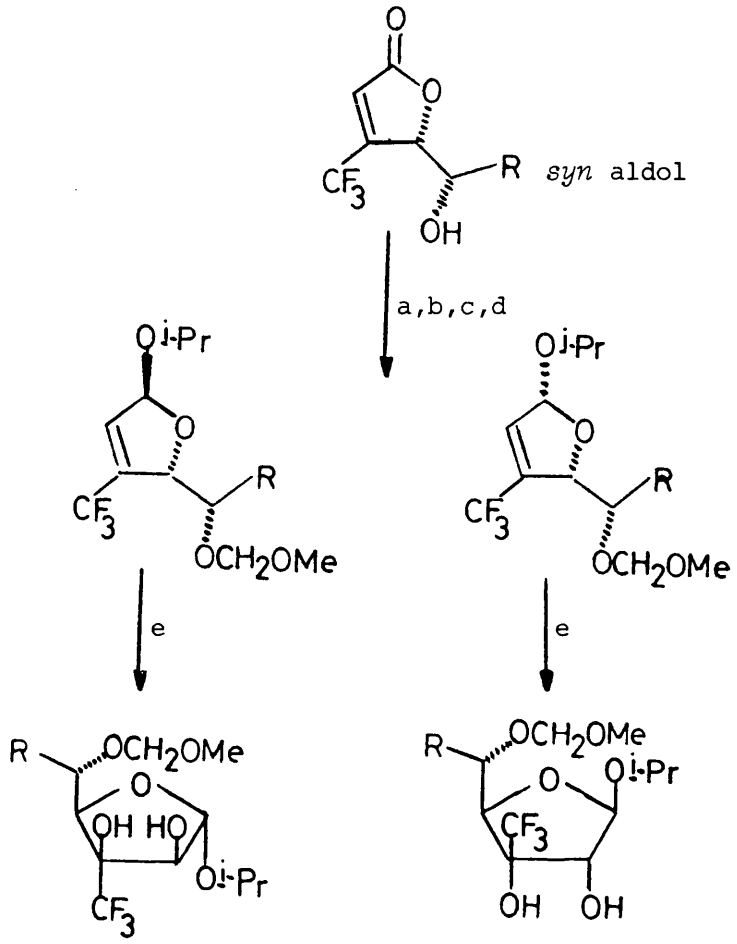


(91)

R	Yield (%)
$PhCH_2OCH_2$	74
$Me(CH_2)_5$	83
$Ph(CH_2)_2$	73

Scheme 76

Only 4-substituted but-2-en-4-olides were produced. ^{1}H n.m.r. and ^{19}F n.m.r. showed the products to be single diastereoisomers. The aldols were identified as *syn* diastereoisomers by *X*-ray analysis of sugars derived from them (Scheme 77).



[a]$MeOCH_2OMe$, P_2O_5; [b]DIBAL-H, toluene; [c]*i*-PrOH, TsOH; [d]separate stereoisomers by chromatography; [e]$KMnO_4$, EtOH.

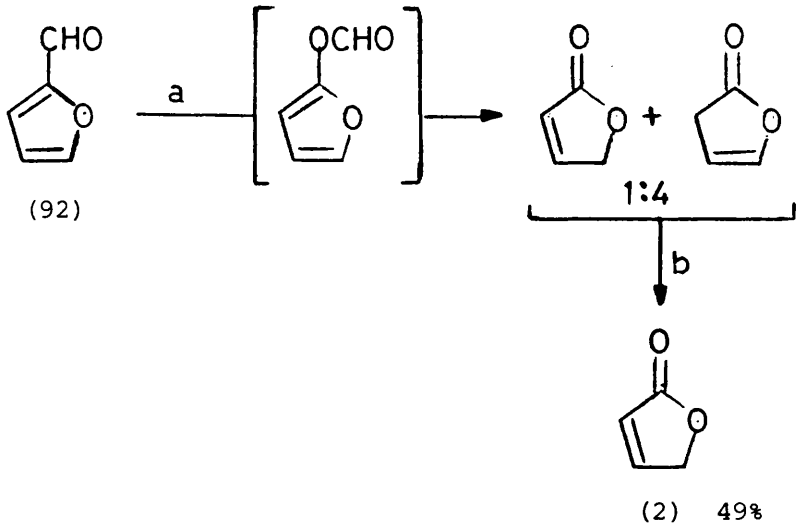
Scheme 77

After publication of our preliminary results on the regioselectivity and stereoselectivity in aldol reactions of 2-(trialkylsiloxy)furans, a similar study was reported by Jefford and co-workers.[75] The Swiss group's findings are similar to those reported by us. In this discussion, the results obtained by Jefford's group are compared and contrasted with the results we obtained.

3.2 Preparation of But-2-en-4-olide and 2-(Trialkylsiloxy)furans

Although both but-2-en-4-olide (2) and 2-(trimethylsiloxy)-furan (88) are commercially available, the high cost of these reagents made it economically desirable to prepare (2) and (88) on a large scale.

But-2-en-4-olide (2) was prepared from the cheap, readily-available furfural (92) by its oxidation with hydrogen peroxide in the presence of formic acid.[76] The desired compound (2) was obtained after distillation in 49% yield (Scheme 78).



(92)

(2) 49%

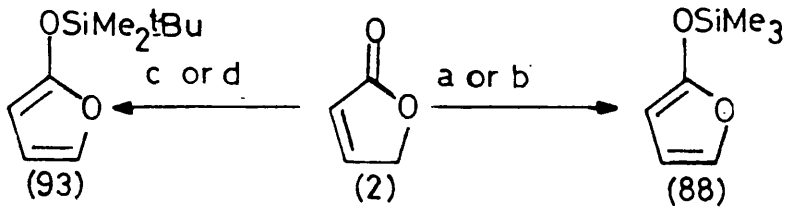
[a] HCO_2H, H_2O_2-H_2O, DCM, $NaHCO_3$; [b] distillation.

Scheme 78

2-(Trialkylsiloxy)furans (88) and (93) were successfully prepared under thermodynamic[77] and kinetic reaction conditions (Scheme 79).

2-(Trimethylsiloxy)furan (88) is particularly sensitive to air and moisture reverting to but-2-en-4-olide (2) on standing in air at room temperature for several hours.

It was reported in section 3.1.2 that the most successful anion reactions of but-2-en-4-olide (2) had been performed under mildly acidic conditions using (88) as the source of the anion.



Reagents and conditions

[a]Kinetic conditions, LDA, THF, -78 °C, 40 min, then Me_3SiCl at -78 °C (typical yield 40%).

[b]Thermodynamic conditions, Et_3N, Me_3SiCl, RT, 4.5 h (typical yield 51%).

[c]Kinetic conditions, LDA, THF, -78 °C, 40 min then t-$BuMe_2SiCl$ at -78 °C (typical yield 50%).

[d]Thermodynamic conditions, Et_3N, t-$BuMe_2SiCl$, RT, 4.5 h (typical yield 25%).

Scheme 79

To begin our examination of the aldol chemistry of but-2-en-4-olide we used (88) as the dienolate.

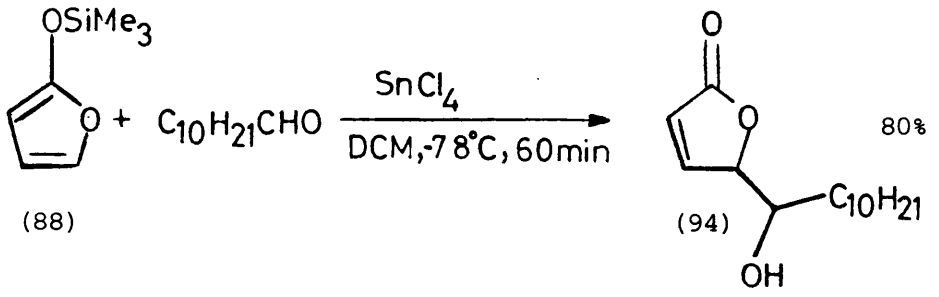
3.3 Lewis Acid-Mediated Aldol Reactions of 2-(Trialkylsiloxy)furans

From earlier studies on the Lewis acid-catalysed aldol reaction of 2-(trialkylsiloxy)furans it was known that the 4-substituted but-2-en-4-olide would be formed under conditions of kinetic control.[72a-c] The relative stereochemistry of the aldol product, however, could not be predicted with certainty, so this had to be rigorously determined.

3.3.1 Assignment of the relative stereochemistry

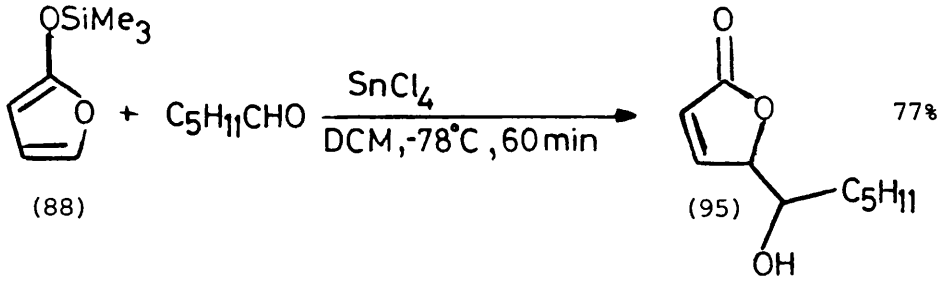
The stannic chloride-catalysed aldol reactions of (88) with undecanal and hexanal are used as examples to demonstrate how the regio- and stereo-structure of the aldol products was determined (Scheme 80).

Both aldol reactions showed good regioselectivity; as expected, only the 4-substituted but-2-en-4-olide was produced. Selected ^1H n.m.r. data on aldols (94) and (95) are shown in Table 26. The H-2 and H-3 resonances occur at chemical shifts



(88) (94)

diastereomeric ratio 98:2



(88) (95)

diasteromeric ratio 98:2

Yields refer to isolated products

Scheme 80

which are characteristic of a but-2-en-4-olide system. The presence of two α,β-enone protons confirmed the aldol products were substituted at C-4.

Table 26

Selected ^{1}H n.m.r. data on 4-substituted but-2-en-4-olides (94) and (95)

Resonance	Chemical shifts δ(ppm)		
	Aldol (94)[a]	Aldol (95)	
	Major isomer[b]	Major isomer[c]	Minor isomer[d]
H-2	6.16	6.16	6.16
H-3	7.50	7.58	7.65
H-4	5.02	5.06	4.98
H-5	3.78	3.83	3.83

[a]No spectral data available on minor diastereoisomer.

[b]Vicinal coupling constant $J_{4,5}$ = 4.5 Hz.

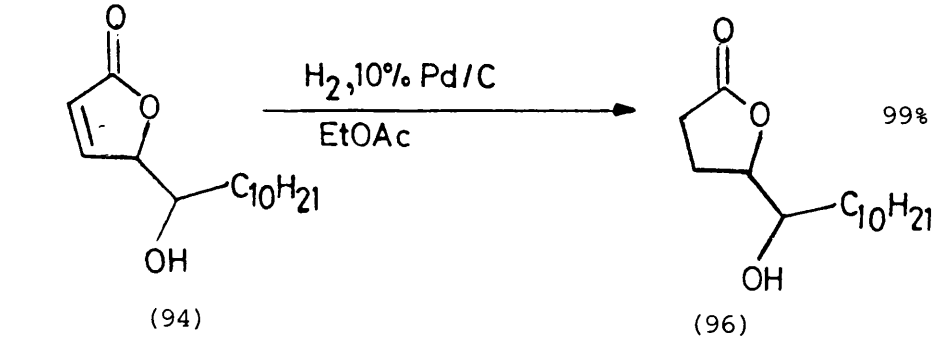
[c]Vicinal coupling constant $J_{4,5}$ = 4.0 Hz.

[d]Vicinal coupling constant $J_{4,5}$ = 5.0 Hz.

The relative stereochemistry of aldols (94) and (95) was more difficult to determine. G.l.c. and ^{13}C n.m.r. analyses of diastereomeric mixtures of each aldol indicated *ca.* 90% of one diastereoisomer.

The ^{1}H n.m.r. chemical shifts and vicinal coupling constants $J_{4,5}$ were very similar for the major and minor diastereoisomers of aldol (95) and hence were of no use in determining the relative stereochemistry of the products (Table 26). Instead, the stereochemistry of the aldol products was determined by chemical correlation with 4-(hydroxyalkyl)-butan-4-olides of known stereochemistry. The major diastereoisomer of aldols (94) and (95) was separated from its minor isomer and then catalytically reduced to 4-substituted butan-4-olides (96) and (97) respectively (Scheme 81).

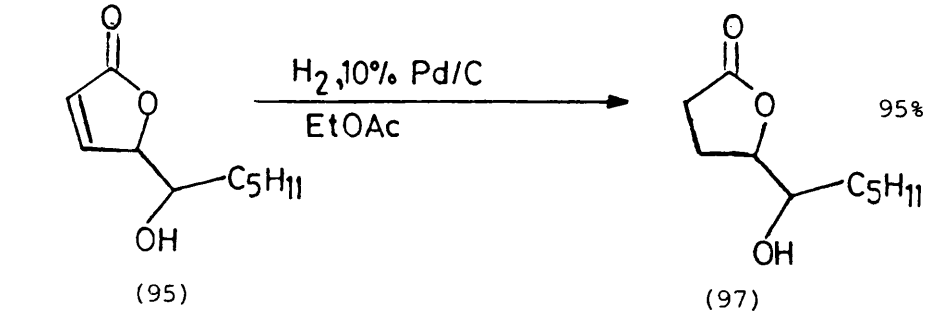
Comparison of the ^{1}H n.m.r. data of (96) with published spectral data for the *syn* and *anti* diastereoisomer of 4-(1'-hydroxyundecyl)butan-4-olide (intermediate in Maramu[78] synthesis of natural product dispalure; see Scheme 82 for synthesis from optically-pure (S)-aspartic acid) showed our compound (96) to be identical to the *syn* diastereoisomer of 4-(1'-hydroxyundecyl)butan-4-olide (Table 27). The major diastereoisomer of 4-substituted but-2-en-4-olide (94), which is the precursor of (96), therefore has *syn* relative stereochemistry.



(94)

single diastereoisomer

(96)



(95)

single diastereoisomer

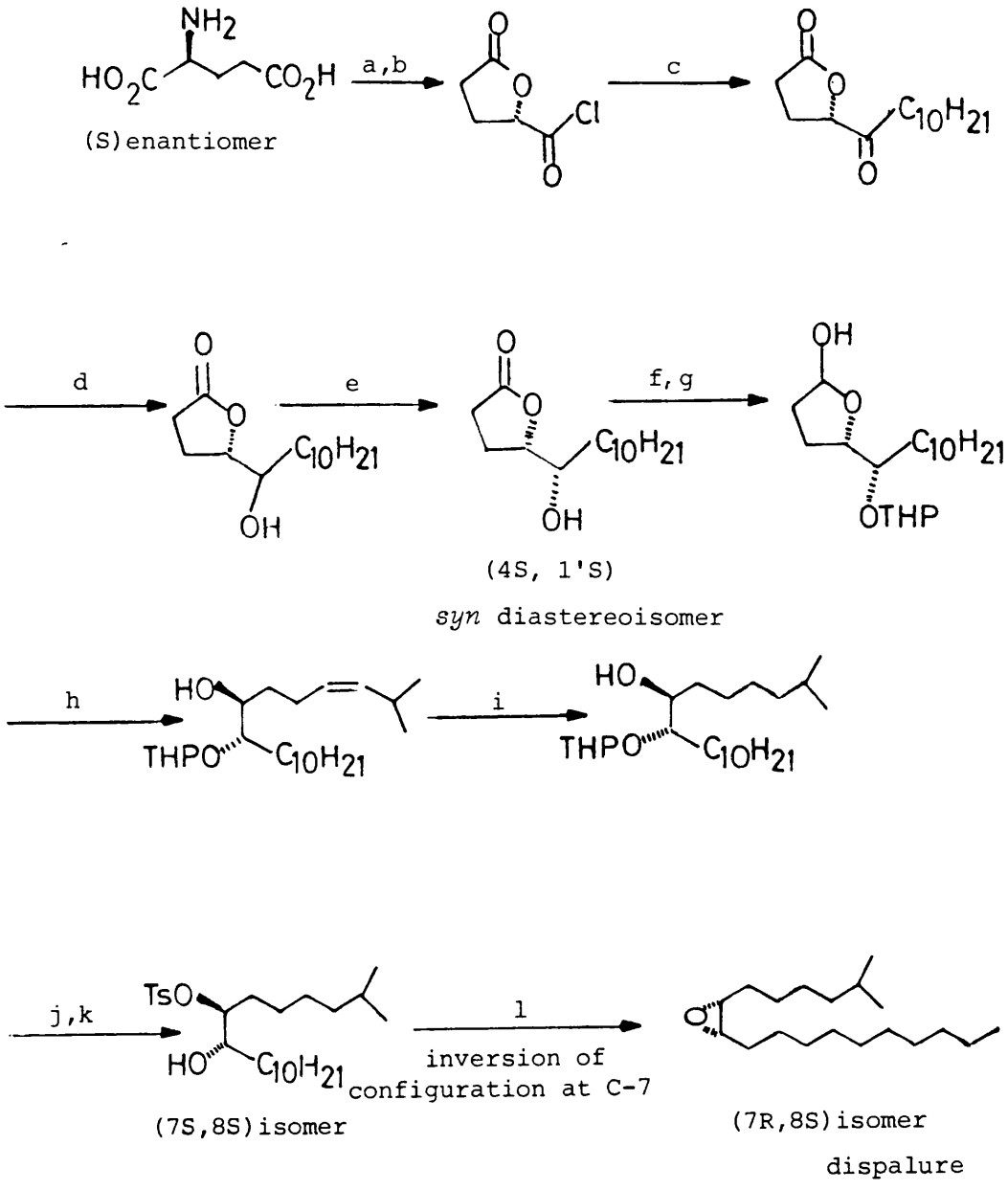
(97)

Scheme 81

Table 27

Correlation of selected ^{1}H n.m.r. data of the major diastereo isomer of aldol (96) with published ^{1}H n.m.r. data on 4-(1'-hydroxyundecyl)butan-4-olide

Chemical shifts (ppm)			
Resonance	Aldol (96)	4-(1'-hydroxyundecyl)butan-4-olide[78]	
		syn diastereoisomer	*anti* diastereoisomer
H-4	4.42	4.46	4.48
H-5	3.58	3.60	3.96



$^{a}HNO_3$, H_3O^+; ^{b}ClCOCOCl, benzene; $^{c}Cd(C_{10}H_{21})_2$, THF; $^{d}NaBH_4$, MeOH; ^{e}separation by chromatography; ^{f}dihydropyran, TsOH; ^{g}DIBAL-H, toluene; $^{h}Ph_3P{=}CH{-}CHMe_2$, THF; $^{i}H_2$, PtO_2, EtOAc; ^{j}TsOH, pyridine; $^{k}H_3O^+$; ^{l}KOH, MeOH.

Scheme 82[78]

A similar chemical correlation study was carried out on the aldol product (97). Comparison of its ^{1}H n.m.r. data with published ^{1}H n.m.r. data for the *syn* and *anti* diastereoisomers of the natural product 4-(1'-hydroxyhexyl)butan-4-olide (L factors; for chiral synthesis from optically pure 2,3-*O*-isopropylidene-*D*-ribose,[79] see Scheme 83) showed aldol (97) to have *syn* stereochemistry (Table 28). The major diastereoisomer of the 4-substituted but-2-en-4-olide (95) therefore has *syn* stereochemistry.

Table 28

Correlation of selected ^{1}H n.m.r. data of the major diastereoisomer of aldol (97) with published ^{1}H n.m.r. data on 4-(1'-hydroxyhexyl)butan-4-olide[79]

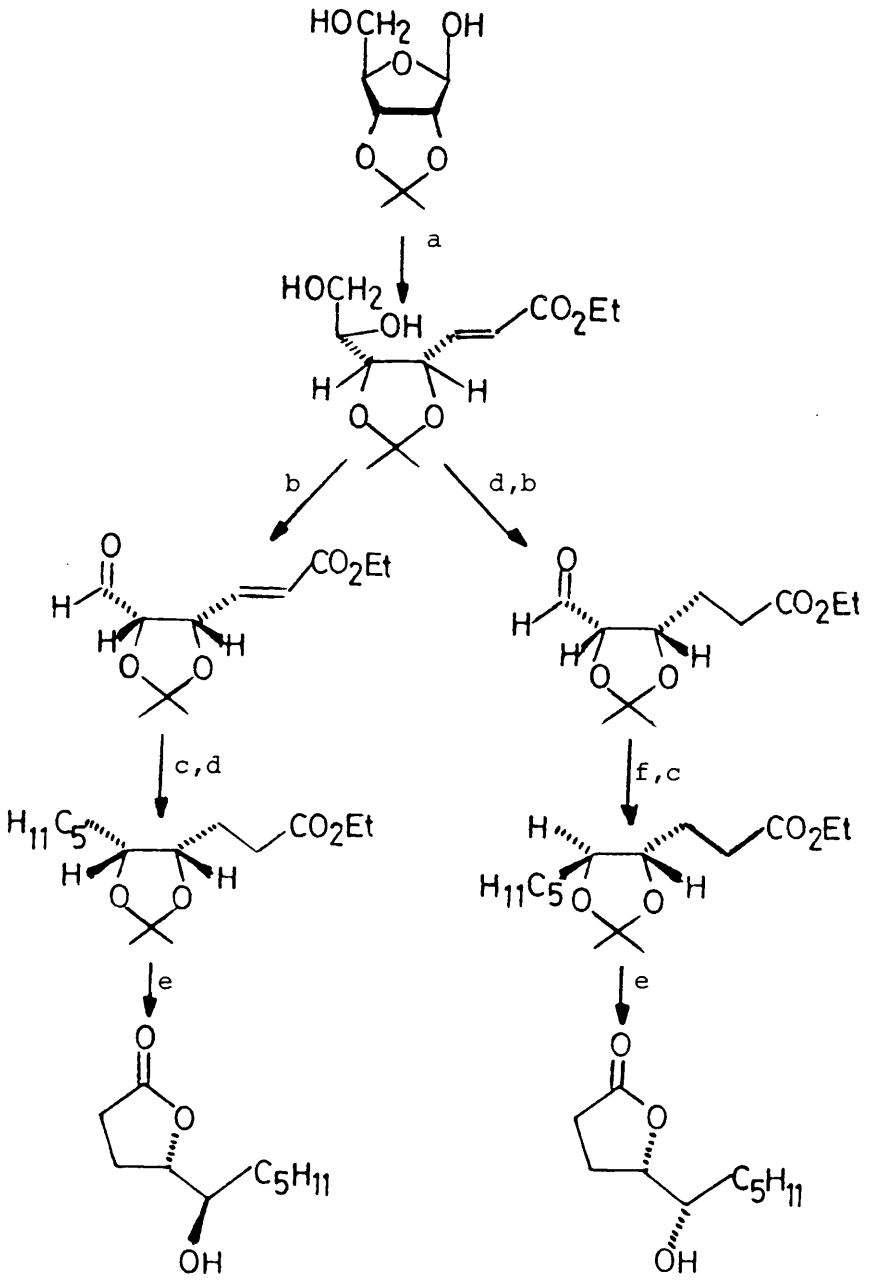
Chemical shifts δ(ppm) and multiplicities (Hz)			
Resonance	Aldol (97)	4-(1'-hydroxyhexyl)butan-4-olide	
		syn diastereoisomer	*anti* diastereoisomer
H-4	4.42, dt (7.5, 4.5)	4.40, dt (7.5, 4.5)	4.42, dt (7.5, 3.5)
H-5	3.57, m	3.56, m	3.94, dt (6.5, 3.5)

3.3.2 *Diastereoselectivity in the stannic chloride-catalysed aldol reaction of 2-(trialkylsiloxy)furans with prochiral aldehydes

One of the first studies describing aldol reactions of 2-(trimethylsiloxy)furan (88) employed stannic chloride to mediate the addition reaction; this reaction was regiospecific; 4-(hydroxyalkyl)but-2-en-4-olides were produced in good yield,[72a-c] (see Section 3.1.2).

To begin our investigation of the diastereoselectivity of the aldol reaction of (88), we decided to use similar reaction conditions. The results of this initial study are shown in Scheme 84 and Table 29.

*Part of this work was performed in collaboration with Mr. Xiao-an Zhang.

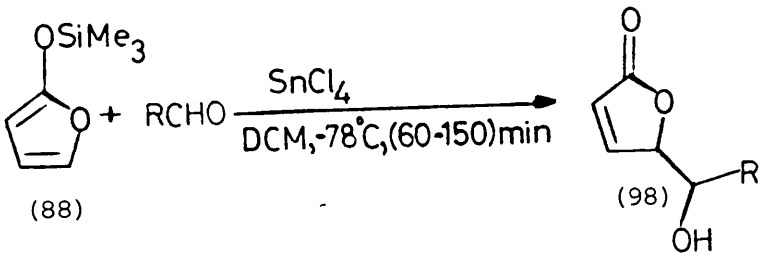


(4S,1'R) *anti* diastereoisomer

(4S,1'S) *syn* diastereoisomer

[a]$Ph_3P{=}CHCO_2Et$, DCM; [b]$NaIO_4$, MeOH; [c]$Ph_3P{=}CHC_3H_7$, THF; [d]H_2, Pd/C, MeOH; [e]H_3O^+; [f]K_2CO_3, MeOH (enolisation)

Scheme 83[79]



(88) (98)

Scheme 84

Table 29

Diastereoselectivity in the $SnCl_4$-mediated aldol reaction of (88) and prochiral aldehydes

Aldehyde RCHO[a]	Aldol product Diastereoisomer ratio[b] *syn:anti*	Yield[c] (%)	Compound
MeCHO	87:13	67	(99)
EtCHO	81:19	52	(100)
$Me(CH_2)_4CHO$	94:6	77	(95)
$Me(CH_2)_9CHO$	98:2	62	(94)
Me_2CHCHO	94:6	80	(101)
Me_3CCHO	70:30	54	(102)
PhCHO	88:12	60	(103)

[a]Diastereomeric ratios and yields refer to typical values. Each aldol addition was performed more than once.

[b]Diastereomeric ratio analysed by g.l.c.

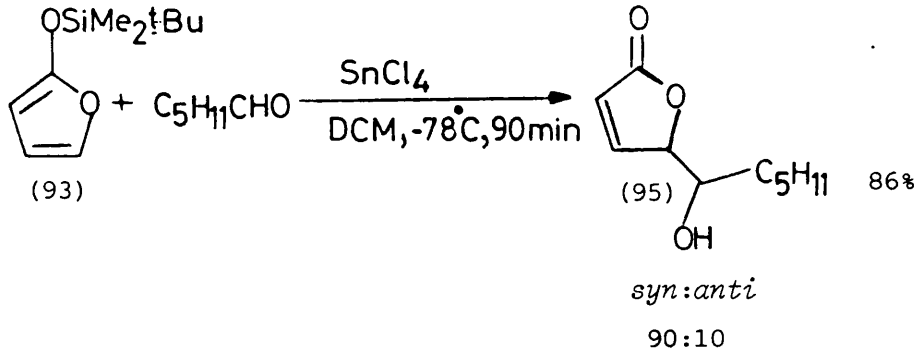
[c]Yields refers to isolated aldols, for g.l.c. yields, correct for recovered (2), see Experimental Section.

All the aldol reactions were regiospecific; only 4-substituted but-2-en-4-olides were produced. The addition reactions also showed good *syn* diastereoselectivity.

The aldol products [(99) - (103)] had spectral data consistent with their proposed structures (see Experimental Section). For information on how the regio- and stereo-structures of the aldol products were determined, see Section 3.3.1. Tables 30 and 31 are used to correlate the ^{1}H n.m.r. and ^{13}C n.m.r. data of the *syn* and *anti* diastereoisomers of 4-(hydroxyalkyl)but-2-en-4-olides.

No dramatic trends emerge in comparing the ^{1}H spectra of the two series other than the H-3 resonances of the *anti* diastereoisomers were slightly downfield from the H-3 resonance of the corresponding *syn* diastereoisomers (δ_{H_3} *anti* > δ_{H_3} *syn*) with the understandable exception of aldol (103) (anisotropic effect of phenyl ring). In the case of the ^{13}C spectra, no clear differences between the two series are apparent.

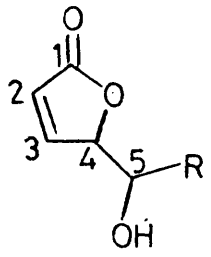
Varying the nature of the siloxy group on the dienolate had very little effect on the diastereoselectivity of the aldol reaction. A stannic chloride-mediated aldol reaction of 2-(*t*-butyldimethylsiloxy)furan (93) and hexanal gave 4-substituted but-2-en-4-olide (95) in 86%, yield (Scheme 85). The diastereomeric ratio of the product (*syn*:*anti* = 90:10) was very similar to that obtained in the corresponding aldol reaction involving (88) and hexanal (*syn*:*anti* = 94:6).



Scheme 85

Table 30

^{1}H N.m.r. chemical shifts in 4-substituted but-2-en-4-olides

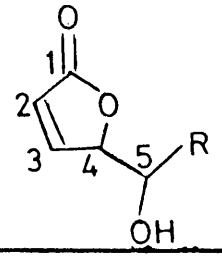


Group R	Chemical shift δ_H (ppm)							
	syn diastereoisomer				*anti* diastereoisomer			
	H-2	H-3	H-4	H-5	H-2	H-3	H-4	H-5
Me	6.20	7.46	4.94	3.94	6.20	7.59	4.96	4.06
Et	6.16	7.56	5.06	3.74	6.16	7.64	4.99	3.75
$Me(CH_2)_4$	6.16	7.58	5.06	3.83	6.16	7.65	4.98	3.83
$Me(CH_2)_9$	6.16	7.50	5.02	3.78		*a*		
Me_2CH	6.18	7.47	5.17	3.45	6.16	7.65	5.09	3.55
Me_3C	6.15	7.48	5.26	3.46	6.17	7.64	5.14	3.54
Ph	6.07	7.32	5.15	4.69	6.13	7.16	5.15	5.05

[a]No spectral data available on *anti* diastereoisomer.

Table 31

^{13}C N.m.r. chemical shifts in 4-substituted but-2-en-4-olides

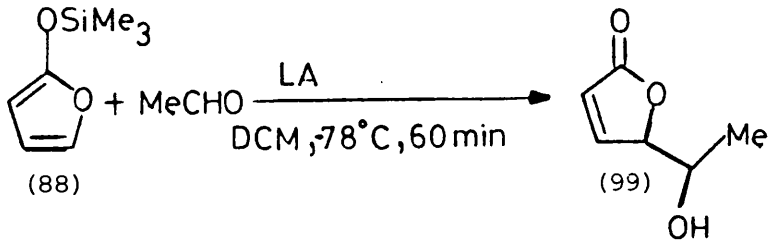


Group R	Chemical shift δ_C (ppm)									
	syn diastereoisomer					*anti* diastereoisomer				
	C-1	C-2	C-3	C-4	C-5	C-1	C-2	C-3	C-4	C-5
Me	173.5	122.9	153.4	87.1	68.3	173.2	122.7	153.6	86.9	67.5
Et	173.5	121.9	154.6	85.9	72.3	173.4	122.0	154.4	86.0	72.4
$Me(CH_2)_4$	173.5	121.9	154.6	86.2	70.8	173.5	122.0	154.4	86.3	71.0
$Me(CH_2)_9$	173.4	122.5	154.3	86.4	71.6			*a*		
Me_2CH	173.4	122.4	154.4	84.6	76.4	173.5	122.2	154.8	84.4	75.9
Me_3C	173.4	121.8	156.0	82.4	77.7	173.5	122.3	155.5	84.2	79.3
Ph	173.5	122.9	153.3	86.6	75.3	173.5	123.1	153.0	86.9	72.9

[a]No spectral data available on *anti* diastereoisomer.

3.3.3 *Diastereoselectivity in the Lewis acid-mediated aldol reaction of 2-(trimethylsiloxy)furan with prochiral aldehydes

The stannic chloride-mediated aldol reactions of (88) were regiospecific and showed good *syn* diastereoselectivity. It was of interest to us to see what effect other Lewis acids would have on the regio- and diastereo-selectivity of the aldol reaction. The results of our study on the aldol reaction of (88) with ethanal, mediated by different Lewis acids under kinetic reaction conditions are cited in Scheme 86 and Table 32.



(88) (99)

Scheme 86

Table 32

Diastereoselectivity in the aldol reaction of (88) and ethanal mediated by Lewis acids

Lewis acid (LA)[a]	Aldol product (99) Diastereoisomer ratio[b] *syn*:*anti*	Yield[c] (%)
$TiCl_4$	63:37	94
$SnCl_4$	87:13	99
$ZnCl_2$	79:21	93
$BF_3.Et_2O$	69:31	85
$AlCl_3$	85:15	60
TMSOTf	89:11	41

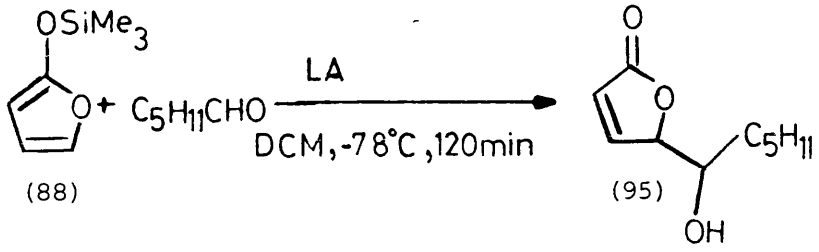
[a](0.1-0.3) equivalents of Lewis acid used to mediate reaction.

[b]Diastereomeric ratio determined by g.l.c. analysis.

[c]Yields determined by g.l.c. analysis using an internal standard sample and correcting for recovered (2).

*Part of this work was performed in collaboration with Mr. Xiao-an Zhang.

A similar study using hexanal as the electrophile has very recently been reported by Jefford and co-workers.[75] Several of the results which they obtained are listed in Scheme 87 and Table 33.



(88) (95)

Scheme 87[75]

Table 33

Diastereoselectivity in the aldol reaction of (88) and hexanal mediated by Lewis acids

Lewis acid (LA)[a]	Aldol product (95) Diastereoisomer ratio[b] *syn:anti*	Yield[c] (%)
$SnCl_4$	76:24	88
$ZnCl_2$[d]	68:32	82
$BF_3.Et_2O$	81:19	95
Ph_3CClO_4[e]	79:21	92
TMSOTf	82:18	95

[a](0.1-0.2) equivalents of Lewis acid used to mediate reaction.
[b]Diastereomeric ratio determined by ^1H n.m.r. analysis (360 MHz)
[c]Yields refer to isolated aldols.
[d]Reaction performed at 0 °C.
[e]Reaction performed at (-78→ 30) °C for 4 h.

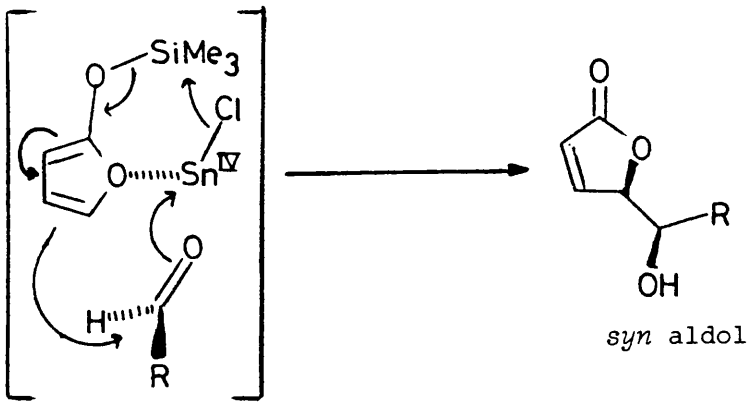
From Tables 32 and 33 it can be seen that the Swiss group obtained very similar results to our own. Varying the Lewis acid did not change the regioselectivity of the reaction, but the level of *syn* diastereoselectivity did change. In our study, stannic chloride was the most effective catalyst, giving high yields and

good *syn* diastereoselectivity. In the Swiss group's study, $BF_3.Et_2O$ was the most efficient catalyst. In both studies, high *syn* diastereoselectivity was conferred by TMSOTf catalyst.

3.3.4 Transition state models used to explain *syn* diastereoselectivity observed in the Lewis acid-mediated aldol reactions of 2-(trimethylsiloxy)furan

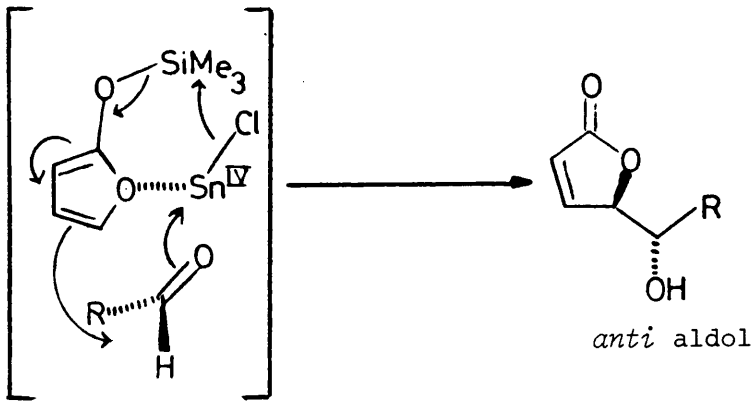
Mechanistically, three transiton state models are proposed to explain the *syn* diastereoselectivity observed in the Lewis acid-catalysed aldol reaction of 2-(trimethylsiloxy)furan (88).

Firstly, a novel tricyclic chelated transition state might be invoked (Figure 23) in which, in a concerted process, the aldehyde is delivered to C-5 of (88) to give the 4-substituted but-2-en-4-olide.[51] The *syn* stereoselectivity results because the *exo* approach of the aldehyde is favoured over *endo* approach for steric reasons.



syn aldol

R *exo* to siloxy furan ring



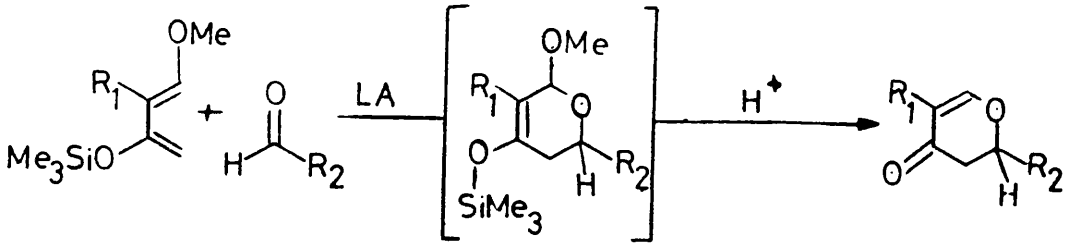
anti aldol

R *endo* to siloxy furan ring

Figure 23

Although the transiton states shown in Figure 23 are useful in explaining diastereoselectivity of aldol reactions in which chelation is possible ($SnCl_4$, $TiCl_4$, $ZnCl_2$ and $AlCl_3$), it cannot be used to explain the *syn* diastereoselectivity observed in reactions employing non-chelating catalysts (TMSOTf, Ph_3CClO_4 and $BF_3.Et_2O$). However, the chelated transiton states should not be discounted, since some reactions may proceed *via* them, for example ($SnCl_4$), and others may proceed *via* alternative transition states.

A second possible transition state model recognises the fact that siloxy butadienes such as (104) are known to be catalysed by Lewis acids to give hetero-Diels-Alder adducts which are unstable in the presence of acid and break down to give derivatives of dihydropyran-4-one (105).[80]



(104) unstable in the presence of H^+ (105)

Scheme 88

It was thought (88) might be reacting *via* similar hetero-Diels-Alder transition states to give intermediates (106) and (107), which would be unstable to acid work-up and break down to give *syn* and *anti* 4-substituted but-2-en-4-olides (Figure 24). *syn* Stereoselectivity would result if *exo* intermediate (106) was favoured over *endo* intermediate (107).

Intermediates (106) and (107) could not be detected by low temperature ^1H n.m.r. monitoring of the reaction [no olefinic resonances between (5.0-5.6) ppm]. Only starting reagents and 4-substituted but-2-en-4-olides were observed.

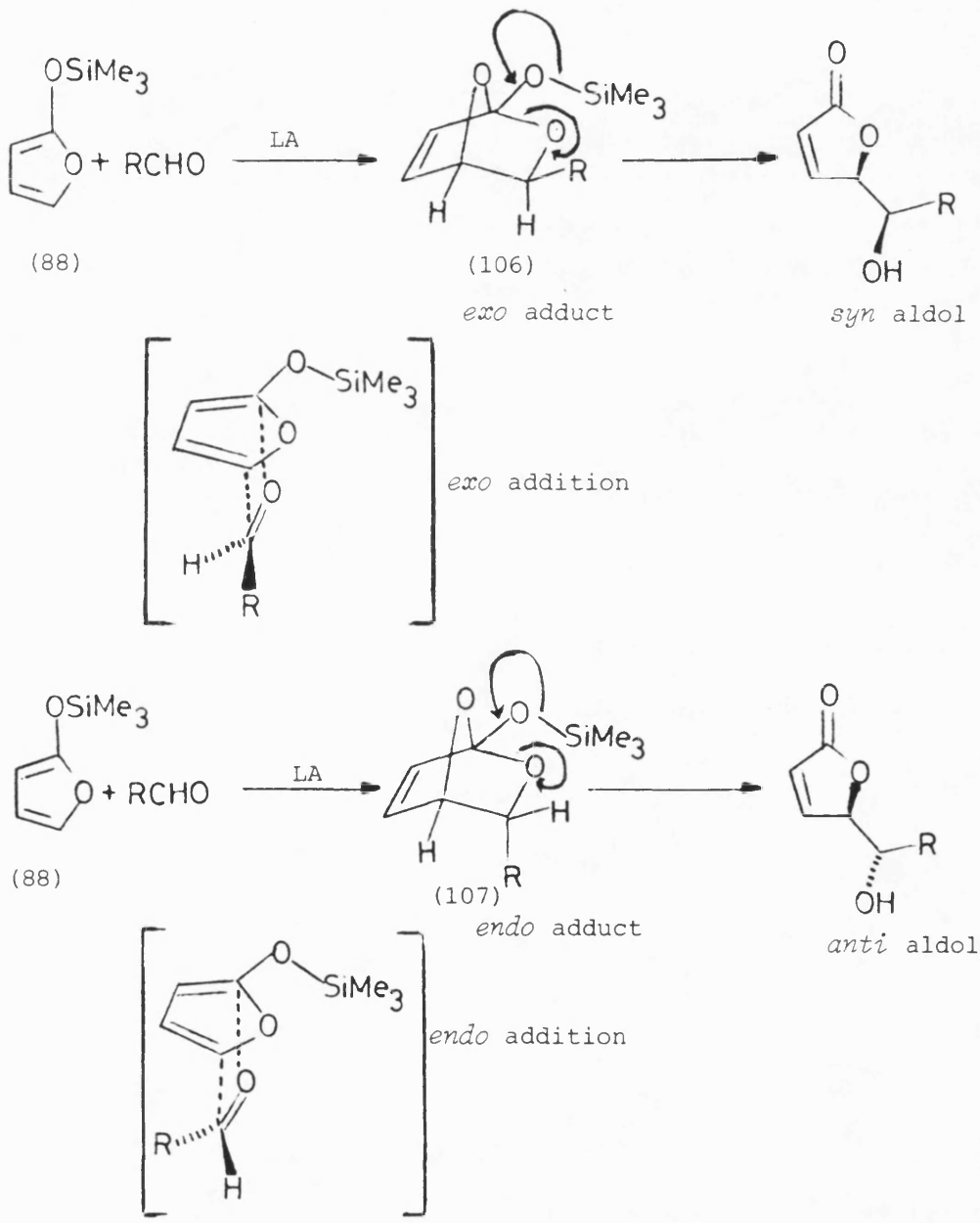

OSiMe3
O + RCHO
LA
SiMe3
R
H
H
O
O
R
OH
(88)
(106)
exo adduct
syn aldol
SiMe3
O
O
H
R
exo addition
OSiMe3
O + RCHO
LA
SiMe3
O
H
H
R
(88)
(107)
endo adduct
anti aldol
SiMe3
O
O
R
H
endo addition

Figure 24

Although there was no conclusive evidence of Diels-Alder type transition states, this route should not be precluded since concentrations of the intermediates (106) and (107) may not have built up to sufficiently high levels to be detected by ^{1}H n.m.r. spectroscopy (270 MHz).

The 'Open Transition State' model depicted in Figure 25 represents the third method by which the *syn* diastereoselectivity of the aldol reaction might be explained; if it is assumed that there is no chelation between the Lewis acid and the siloxy furan, the Lewis acid only co-ordinates to the aldehyde, at a site *anti* to the R group.[10a,75] Competition between the six staggered conformations of the open transition state depends just on steric and electronic factors. The two most favoured conformations are thus A' and C. Since the former would be Diels-Alder-like and have additional stabilising secondary orbital interactions, it is favoured and *syn* selectivity results.

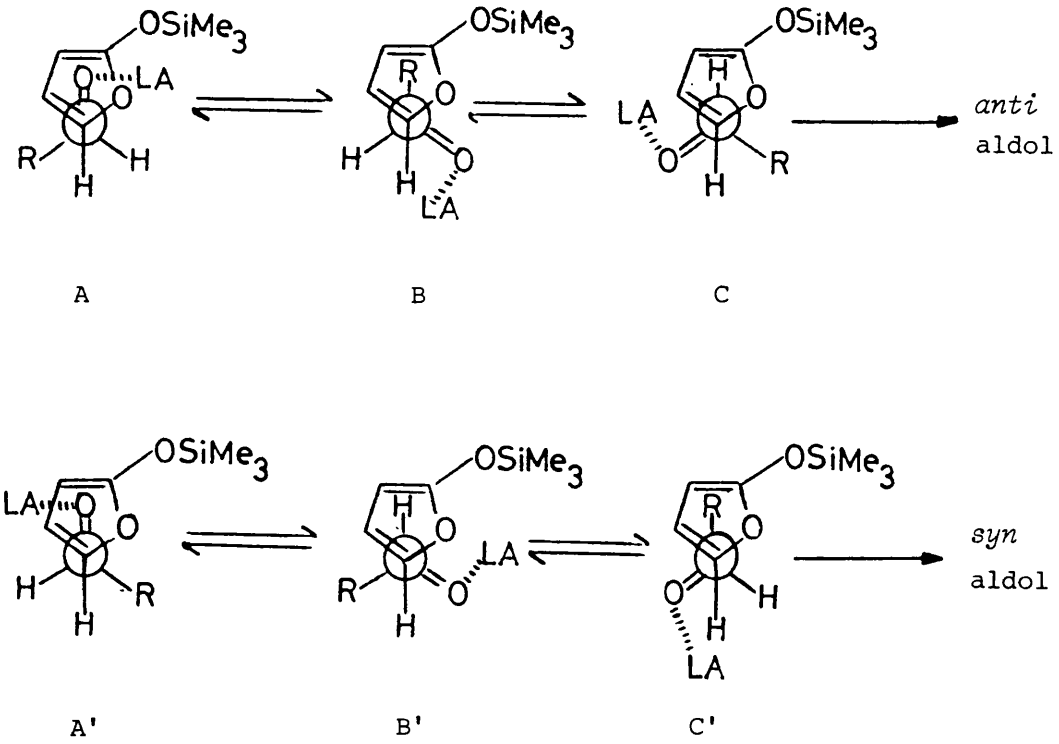
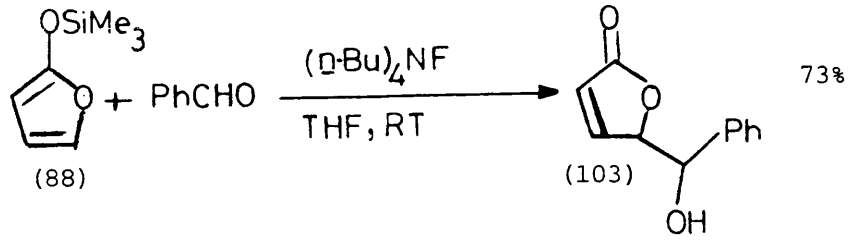


Figure 25

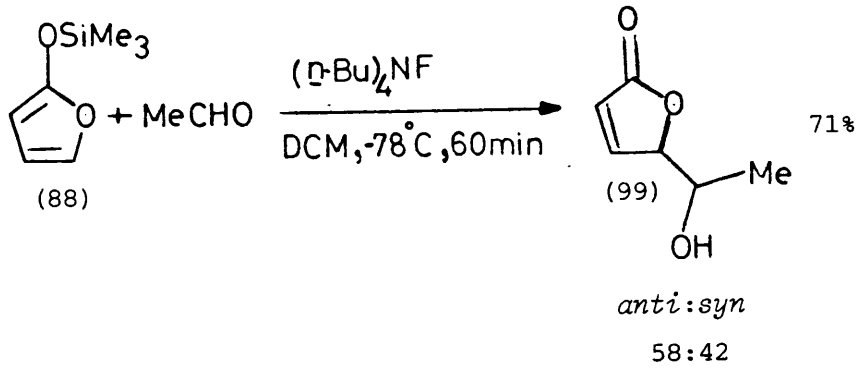
3.4 Fluoride Ion-Catalysed Aldol Reactions of 2-(Trimethylsiloxy)furan

Ricci and co-workers,[77a] have recently shown that the aldol reaction of (88) may be mediated by fluoride ion (Scheme 89). The addition reaction was regiospecific giving only a 4-substituted but-2-en-4-olide (103). No information was given on the relative stereochemistry of the aldol product.



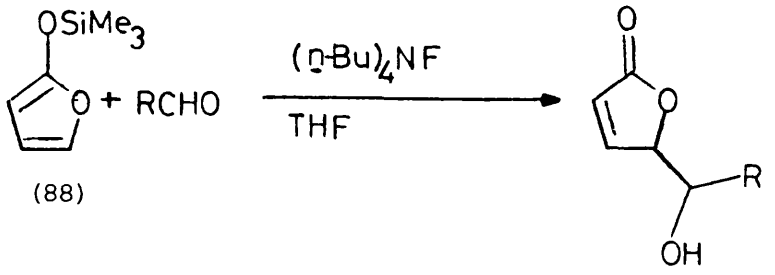
Scheme 89

We have examined the diastereoselectivity of the fluoride ion-mediated aldol reaction of (88) using ethanal as the electrophile[51] (Scheme 90). The 4-substituted but-2-en-4-olide (99) was produced in 71% yield. The addition reaction showed poor diastereoselectivity; a 58:42 mixture of *anti*:*syn* aldols was obtained. [Compare this with Lewis acid-mediated aldol reactions of (88) which generally showed good *syn* diastereoselectivity, Table 32.]



Scheme 90

Jefford and co-workers[75] have also studied the fluoride ion-catalysed aldol reaction of (88) under kinetic and thermodynamic conditions. Better levels of *anti* diastereoselectivity were observed (Scheme 91 and Table 34).



(88)

Scheme 91

Table 34

anti Diastereoselectivity observed in the fluoride ion-catalysed aldol reaction of (88)

Aldehyde RCHO	Reaction Conditions	Aldol product Diastereomeric ratio[a] *anti*:*syn*	Yield[b] (%)
Me_2CHCHO	-78 °C, 6h	87:13	77
	(-78 → 20) °C, 48h	78:22	64
Me_3CCHO	(-78 → 45) °C, 8h	92:8	48
	(-78 → 20) °C, 23h	88:12	36

[a]Diastereomeric ratio determined ^1H n.m.r. (360 MHz).
[b]Yields are of isolated diastereomeric mixtures.

The variable levels of *anti* diastereoselectivity observed between Jefford's study and our study for the fluoride ion-catalysed aldol reaction of (88) may be explained by an open transition state model (Figure 26).

In fluoride ion-catalysed aldol reactions, there can be no chelation between the aldehyde and siloxyfuran. Desilylation results in the formation of a 'naked dienolate'. The negative charge on this dienolate is better dispersed in conformations in which the oxygens of the dienolate and aldehyde are as far apart as possible.

Transition state conformers B, C and B', C' are favoured. The stereoselectivity of the reaction depends only on steric interactions between R and the dienolate ring. Conformation C is preferred when R is sterically demanding and the reaction shows good *anti* selectivity. R = *t*-Bu and *i*-Pr in Jefford's study resulted in good stereoselectivity, which is only slightly modified under the equilibrating condition shown in Table 34.

When R is sterically subordinate, the interaction with the dienolate ring is small, and there is little energy difference between the transiton state conformers B, C and B', C' and poor diastereoselectivity is observed. (R = Me in our study resulted in poor diastereoselectivity.)

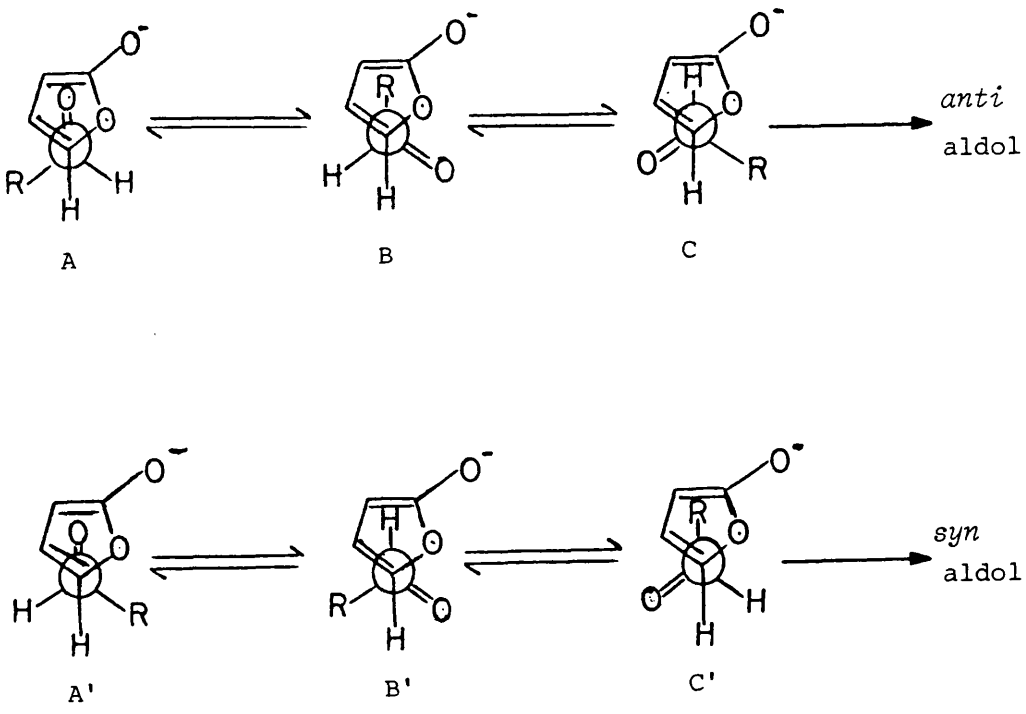
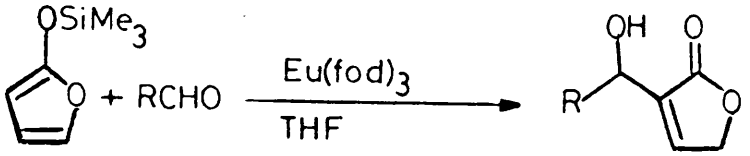


Figure 26

3.5 *Lanthanide Reagent-Catalysed Aldol Reactions of 2-(Trimethylsiloxy)furan

It has been reported by Danishefsky and co-workers[81] that the lanthanide reagent $Eu(fod)_3$ is able to act as a mild Lewis acid and catalyse hetero-Diels-Alder reactions. Since one of the transition state models proposed to explain the *syn* diastereoselectivity of the Lewis acid-mediated aldol reaction of (88) involved the formation of an intermediate Diels-Alder adduct, it was of interest to see what effect $Eu(fod)_3$ would have on the aldol reaction. The results of the study are listed in Scheme 92 and Table 35.



(88) (108)

Scheme 92

Table 35

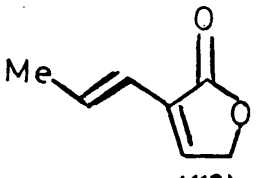
Aldol reaction between (88) and prochiral aldehydes catalysed by $Eu(fod)_3$

Aldehyde RCHO	Reaction conditions	Aldol product Yield (%)[a]	Aldol product Compound
MeCHO[b]	RT, 168 h	68	(109)
EtCHO[c]	40 °C, 72 h	54	(110)
Me_2CHCHO[b]	60 °C, 48 h	65	(111)
PhCHO[b]	60 °C, 48 h	73	(112)

[a]Yields determined by g.l.c. analysis (internal standard), and were corrected for recovered but-2-en-4-olide.

[b]Small amounts of multi-component by-product were unidentified, no 4-substituted but-2-en-4-olide was detected by g.l.c. analysis of crude product.

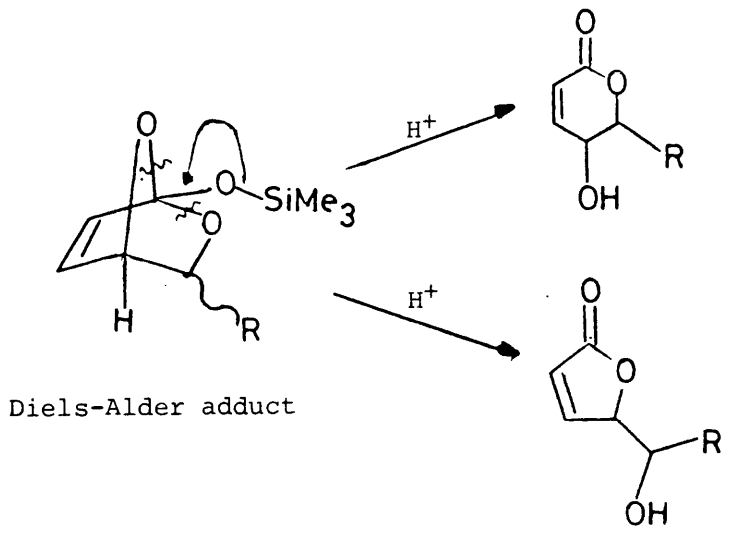
[c]Dehydration product (E)-2-(prop-1'-enyl)but-2-en-4-olide (113) was also produced in 21% yield.



(113)

*Part of this work was performed in collaboration with Mr. Xiao-an Zhang.

No 4-(hydroxyalkyl)but-2-en-4-olides or 5-alkyl-4-hydroxy-pent-2-en-5-olides which would result from acid hydrolysis of the intermediate Diels-Alder adduct shown in Scheme 93, were detected. Instead, only 2-substituted but-2-en-4-olides were produced.



Diels-Alder adduct

Scheme 93

The 2-substituted but-2-en-4-olides (109 → 112) were identified primarily from their ^{1}H n.m.r. spectra. Each spectrum showed only one olefinic proton at *ca.* δ 7.4, which suggested substitution at C-2 of the but-2-en-4-olide. The H-4 resonance of the product at *ca.* δ 4.8 integrated to two protons, indicating that there was no substituent at C-4.

The ^{1}H n.m.r., ^{13}C n.m.r., i.r. and mass spectra data of the products were consistent with a 2-substituted but-2-en-4-olide (see Tables 36 and 37 and Experimental section).

The results cited in Table 35 suggest that the reaction is not proceeding *via* a Diels-Alder mechanism, but more likely *via* a $Eu(fod)_3$-chelated aldol reaction in which addition occurs from C-3, rather than C-5 of the siloxyfuran (88), to give, initially, a 2-substituted but-3-en-4-olide (114), which equilibrates under the reaction condtions (RT → 40 °C for 2 → 7 days) to the thermodynamically more stable 2-substituted but-2-en-4-olide (108).

Table 36

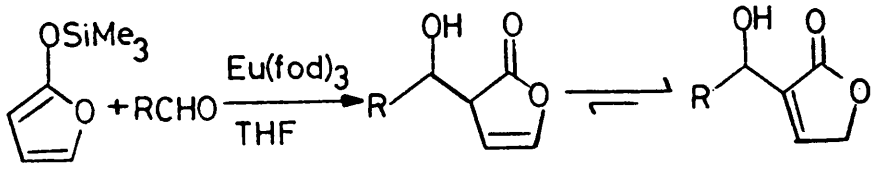
^{1}H N.m.r. chemical shifts in 2-substituted but-2-en-4-olides

Group R	Chemical shifts δ (ppm)		
	H-3	H-4	H-5
Me	7.37	4.88	4.53
Et	7.38	4.86	4.46
Me_2CH	7.37	4.65	4.30
Ph	7.18	4.72	5.50

Table 37

^{13}C N.m.r. chemical shifts in 2-substituted but-2-en-4-olides

Group R	Chemical shifts δ (ppm)				
	C-1	C-2	C-3	C-4	C-5
Me	173.2	136.0	145.2	70.8	63.2
Et	173.2	136.2	145.3	70.4	68.0
Me_2CH	173.3	135.3	146.2	70.5	72.0
Ph	173.1	136.3	146.4	70.7	69.0

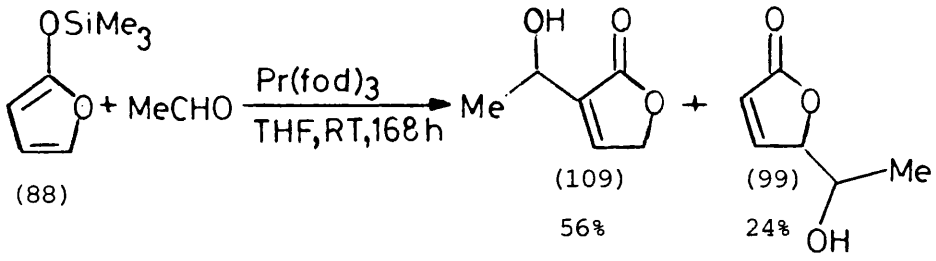


(88) (114) (108)

Scheme 94

No literature precedent exists for the discovery that lanthanide reagents can mediate aldol reactions. The reason why their behaviour differs from Lewis acids as regards regio-selection at C-3, instead of C-5 of (88), is still unclear; (α- *v* γ-substitution).

Since the lanthanide reagent $Pr(fod)_3$ responds differently to $Eu(fod)_3$ in n.m.r. measurements, it was of interest to see if there would be some difference between them in mediating the aldol reaction of (88) (Scheme 95).

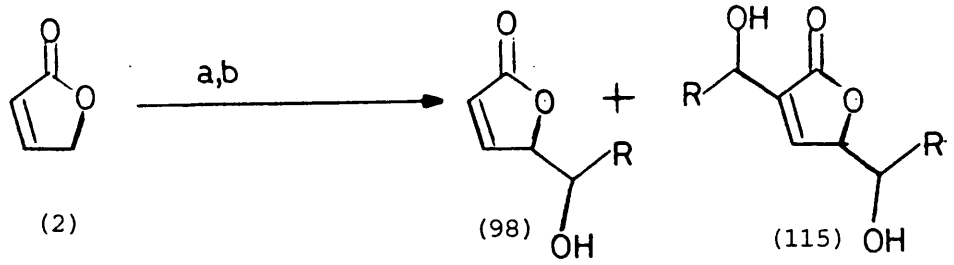


Scheme 95

The lanthanide reagent $Pr(fod)_3$ was found to act in a similar fashion to $Eu(fod)_3$ giving mainly the 2-substituted but-2-en-4-olide (109); but the reaction was not as regio-selective, since a significant amount of the 4-substituted but-2-en-4-olide (99) was also produced.

3.6 Aldol Reactions of But-2-en-4-olide mediated by Lithium Di-isopropylamide

Previous studies on the base-mediated aldol reaction of but-2-en-4-olide had suggested that the reaction showed poor regio-selectivity, mixtures of poly-substituted but-2-en-4-olides were often produced (see Section 3.1.1). Despite these adverse literature reports and in view of our success with the LDA-mediated aldol reaction of cyclopent-2-enone, we decided to investigate the LDA-mediated reaction of but-2-en-4-olide. The results of this study are cited in Scheme 96 and Table 38.



[a]LDA, THF, -78 °C, 10 min; [b]RCHO, THF, -78 °C, 65 min.

Scheme 96

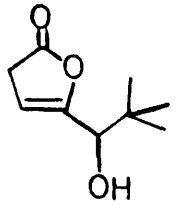
Table 38

Regioselectivity in the LDA-mediated aldol reaction of but-2-en-4-olide

Aldehyde RCHO	Aldol products[a] 4-substituted but-2-en-4-olide : 2,4-disubstituted but-2-en-4-olide		
Me_3CCHO[b]	(102)	80: 4	(116)
Me_2CHCHO	(101)	74:26	(117)
$Me(CH_2)_4CHO$	(95)	34:66	(118)
EtCHO	(100)	27:73	(119)

[a]Ratios (%) determined by ^1H n.m.r. analysis of crude mixture.

[b]4-(1'-hydroxy-2,2'-dimethylpropyl)but-3-en-4-olide (120) was also present in 16% of crude mixture.



(120)

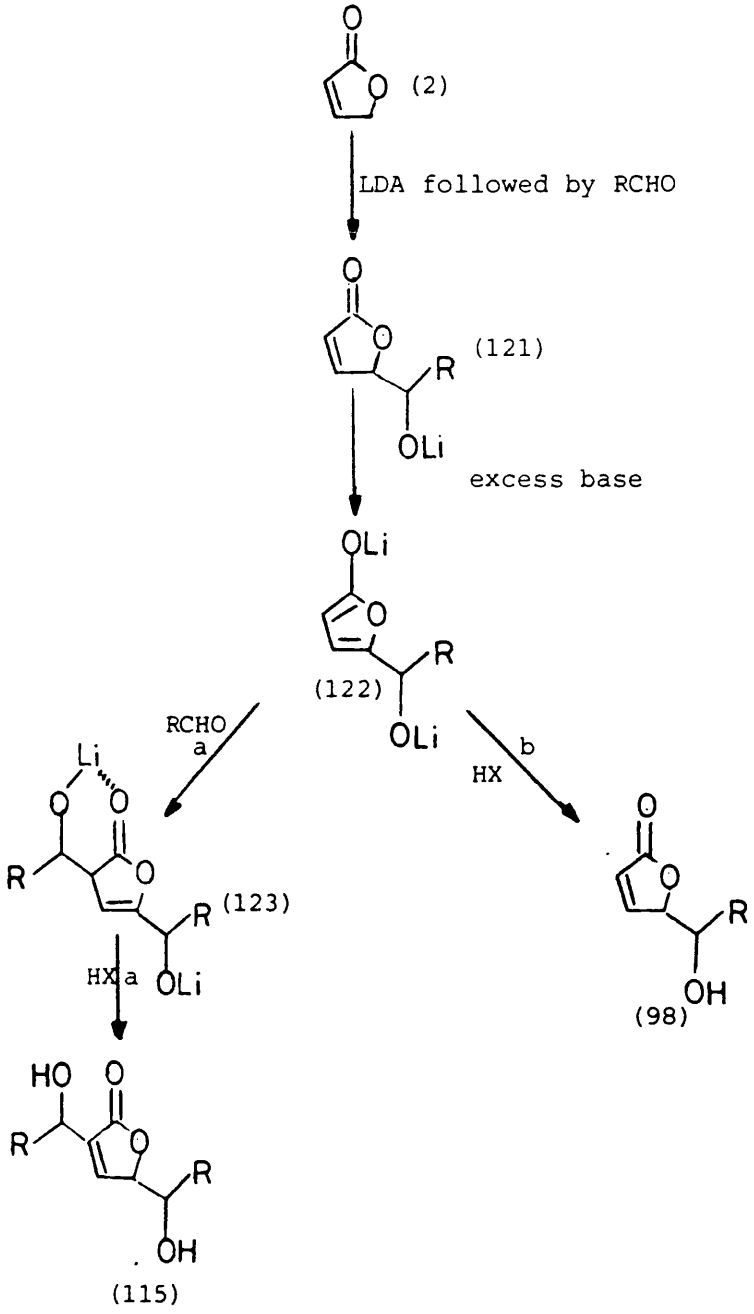
The base-mediated aldol reaction of (2) exhibited variable levels of regioselectivity, mixtures of 4-(hydroxyalkyl)but-2-en-4-olides and 2,4-di(hydroxyalkyl)but-2-en-4-olides were formed. As the steric bulk of the aldehyde was increased, greater amounts of the mono-substituted but-2-en-4-olide were formed. Mixtures of diastereoisomers were produced for both 4-substituted but-2-en-4-olides and 2,4-disubstituted but-2-en-4-olides. Poor diastereoselectivity was observed in the aldol reactions, the *anti* aldol being the major diastereoisomer for the mono-substituted aldol. This contrasts with Lewis acid-mediated aldol reactions of (88) which showed good *syn* diastereoselectivity.

One possible explanation for the poor regioselectivity of the addition reactions is shown in Scheme 97.

The aldol addition initially occurs at C-4 of (2), to give the base-labile intermediate (121), which, in the presence of excess base, gives the dianion intermediate (122). This intermediate might react with a second molecule of aldehyde to give a 2,4-disubstituted but-3-en-4-olide intermediate (123), which isomerises under basic conditions to the thermodynamically more stable conjugated regio-isomer (115) (pathway a), or with the quenching reagent HX to give the 4-substituted but-2-en-4-olide (98) (pathway b).

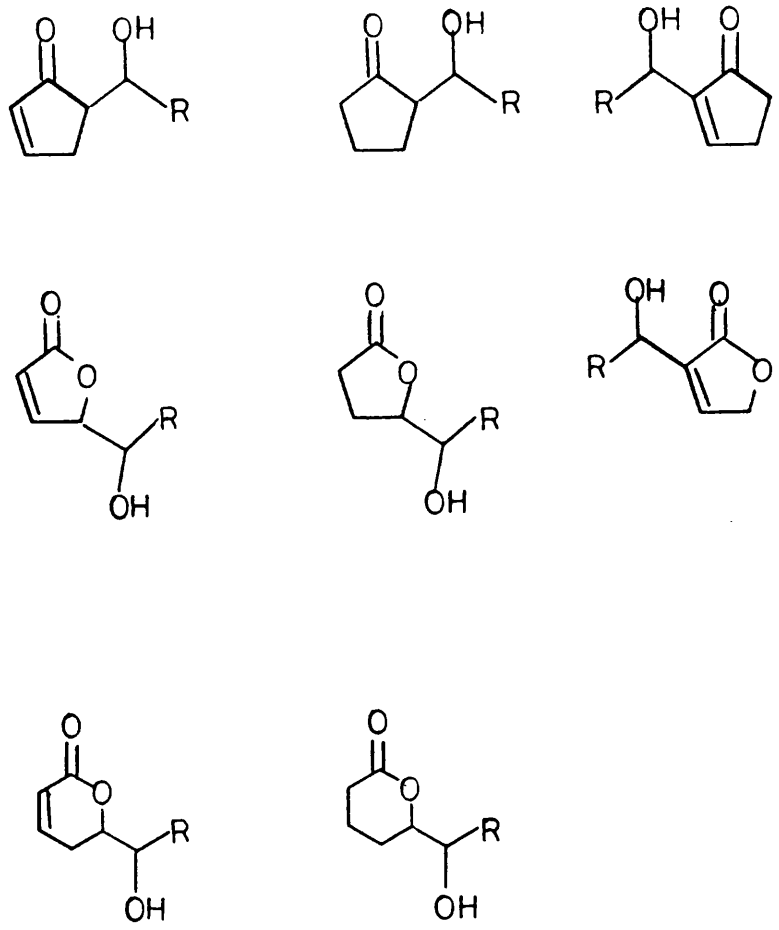
As the steric bulk of the aldehyde increases, pathway (a) might be slower than pathway (b) hence a smaller proportion of the 2,4-disubstituted but-2-en-4-olide (115) would be produced.

Support for the pathways shown in Scheme 97 comes from the fact that the LDA-mediated reaction of (2) with 2,2-dimethylpropanal gave 4-(1'-hydroxy-2',2'-dimethylpropyl)but-3-en-4-olide (120) (16%), as well as the 2,4-disubstituted but-2-en-4-olide (116) (4%) and 4-substituted but-2-en-4-olide (102), (80%). Aldol (120) may have resulted from quenching reagent HX, reacting with intermediate (121) (R = Me_3C) at C-3. No 4,4-disubstitued but-2-en-4-olides were produced, presumably for steric reasons. The 4-substituted but-2-en-4-olide and 2,4-disubstituted but-2-en-4-olides had spectral data consistent with their proposed structures.


(2)
LDA followed by RCHO
(121)
excess base
(122)
RCHO
a
b
HX
(123)
HX a
(98)
(115)

Scheme 97

In conclusion, the aldol chemistry discussed in Chapters 2 and 3 provides a simple and efficient method for the stereo-controlled construction of the series of cyclic systems depicted in Scheme 98. It is hoped that this methodology will find many practical applications in syntheses.



Scheme 98

EXPERIMENTAL

EXPERIMENTAL

Solvents and techniques for anion reactions

Petroleum ether (petrol) refers to petroleum spirit, b.p. range 60-80 °C and ether refers to diethyl ether. Reaction solvents were dried and distilled before use, as were solvents used for chromatography. Tetrahydrofuran (THF) was pre-dried over sodium wire and then refluxed over sodium benzophenone ketyl until dry and re-distilled prior to use. Dichloromethane (DCM) was dried by distillation from calcium hydride.

All glassware and apparatus used in organolithium reactions were dried overnight in an oven at 125 °C, then allowed to cool in a dessicator. The flasks were sealed with rubber septums and flame dried before use. All reactants were transferred with syringes and needles. The anion reactions were performed under dry argon or nitrogen atmospheres.

Chromatography

Reactions were monitored by thin layer chromatography (t.l.c.) on Merk DC-alufolien plates coated with either Kiesel gel 60 F_{254} or aluminium oxide 60 F_{254}. Visualisation of reaction components was achieved by illumination under short wavelength (254 nm) ultraviolet light and/or spraying with any one of:-

(a) 7% (w/v) methanolic solution of phosphomolybdic acid (PMA).
(b) 0.5% (w/v) aqueous potassium permanganate solution.
(c) 5% (w/v) dinitrophenylhydrazine in 9:2:1 H_2O:MeOH:H_2SO_4 solution.
(d) Iodine vapour.

Column chromatography was performed using short path pressurised columns packed with silica gel (Merk 7747) for medium pressure chromatography and (Merk 9385) for flash chromatography. Diastereoisomer ratios were determined by temperature-programmed gas-liquid-chromatography (g.l.c.).

Spectroscopy

Nuclear magnetic resonance (n.m.r.) spectra were recorded at 270 MHz (^1H) or 67.8 MHz (^{13}C) unless otherwise stated. All spectra were run in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as internal standard unless otherwise stated. Chemical shifts (δ) are expressed as downfield

shifts from TMS with multiplicities denoted by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), dd (doublet of doublets), dt (doublet of triplets), bs (broad singlet), m (multiplet) and bm (broad multiplet). Infrared (i.r.) spectra were recorded as liquid film or $CHCl_3$ solutions with the absorption frequencies (ν) expressed in cm^{-1}. Mass spectra (m.s.) were recorded using electron impact (E.I.) and/or chemical ionisation (C.I. reagent gas isobutane) techniques. All melting points (m.p.s) are uncorrected. Elemental microanalyses and accurate mass measurements were obtained from the Physical and Chemical Measurement Unit (University of Bath).

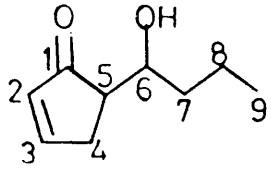
Instrumentation

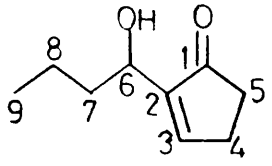
^1H N.m.r.	Jeol GX FT 400 (400 MHz)
	Jeol GX FT 270 (270 MHz)
	Jeol PS 100 (100 MHz)
	Varian EM-360 (60 MHz)
	Hitachi Perkin-Elmer R24 (60 MHz)
^{13}C N.m.r.	Jeol GX FT 270 (67.8 MHz)
	Jeol FX 90Q (22.5 MHz)
I.r.	Perkin-Elmer 197 and 1310 grating
M.s.	VG 7070E with 2000 data system
M.p.	Electrothermal MKII
G.l.c.	A.I. Model 93 gas chromatograph

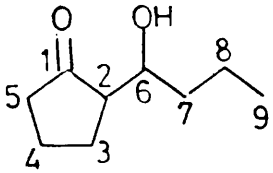
EXPERIMENTAL TO CHAPTER 2

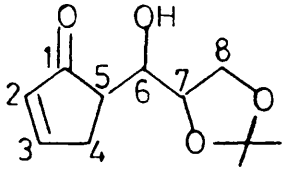
Aldol Chemistry of Cyclopent-2-enone and its Silyl Dienolate

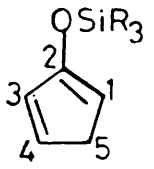
For convenience, when considering spectra, the compounds discussed in this section are numbered as exemplified below. However, elsewhere when numbering compounds, the IUPAC nomenclature and numbering has been used.

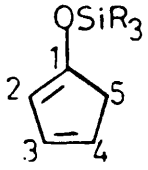


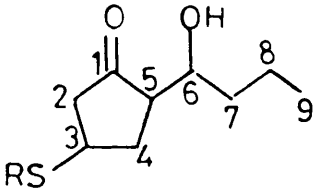


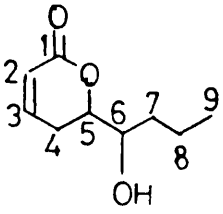












General Procedure for Aldol Reactions between Cyclopent-2-enones and Aldehydes mediated by LDA (kinetic conditions)

To a stirred solution of di-isopropylamine (1.45 cm^3, 11.0 mmol) in freshly distilled THF (15 cm^3) at 0 °C under a nitrogen atmosphere, was added *n*-butyllithium (11.0 mmol). After 10 min the solution was cooled to -78 °C and cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol) in dry THF (5 cm^3) was added dropwise. After stirring for *ca.* 35 min, the aldehyde (11.0 mmol) in dry THF (5 cm^3) was added and the mixture stirred at -78 °C for a further 30-60 min. The reaction was then quenched with saturated aqueous ammonium chloride (8 cm^3) and allowed to warm to ambient temperature. The solvent was removed by evaporation to give a creamy suspension which was diluted with ether (100 cm^3). The ethereal solution was washed with brine (2 x 30 cm^3), the organic layers collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave an oily residue which was purified by column chromatography (silica gel) to afford a diastereomeric mixture of aldol adducts.

The diastereoisomer ratios of the crude products were determined by g.l.c. and/or n.m.r. spectroscopy. All the LDA-mediated aldol reactions of (1) were performed more than once and the yields and diastereoisomer ratios quoted refer to the average or most typical result. The regiostructure of the aldol products was determined from their ^1H n.m.r., ^{13}C n.m.r., i.r. and mass spectral data (Section 2.2.1). The relative stereochemistry of the products was provisionally assigned on the basis of ^1H n.m.r. coupling constants ($J_{5,6}$ *anti* > $J_{5,6}$ *syn*). Unequivocal evidence of the regio- and stereo-structures of the aldol products was obtained by converting them to 2-substituted cyclopentanones of known stereochemistry (Section 2.2.2).

The following aldols have been prepared by the foregoing general procedure.

5-(1'-Hydroxy-1'-phenylmethyl)cyclopent-2-enone (35).-Starting with cyclopent-2-enone (1) (0.42 cm^3, 5.0 mmol), distilled benzaldehyde (0.56 cm^3, 5.5 mmol) and following the general procedure for LDA-mediated aldol reactions of cyclopent-2-enones (reaction time 60 min), the *title compound* (35) (0.67 g, 71%) was obtained as a yellow syrup after column chromatography [silica gel, petrol-EtOAc (1:1)]. G.l.c. analysis of a sample of the crude mixture gave a *syn*:*anti* diastereoisomer ratio of 26:74.

A sample of aldol (35) was separated into its *syn* and *anti* isomers by flash chromatography [silica gel, DCM-EtOAc (8:2)]. *anti* Diastereoisomer *[5RS,1'SR]-5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone*, yellow oil; ν_{max} ($CHCl_3$) 3460 (OH), 3030-3000, 1680 (CO), 1585 (C=C), 1400, 1340 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.18 (1H, dq, J = 20.0, 2.5 Hz, H-4a), 2.42 (1H, ddt, J = 20.0, 7.5, 2.5 Hz, H-4b), 2.64 (1H, ddd, J = 9.5, 7.5, 2.5 Hz, H-5), 4.58 (1H, d, J = 9.5 Hz, H-6), 4.66 (1H, bs, OH), 6.12 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.14-7.28 (5H, m, H-aromatic), 7.60 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 32.6 (C-4), 50.8 (C-5), 75.2 (C-6), 126.9, 128.2, 128.6, 141.3 (C-aromatic), 133.6 (C-2), 165.3 (C-3), 212.6 (C-1); m/z (C.I.) 189 $(M+1)^+$, 171 $(M+1-H\ O)^+$, 107, 83; [Found: C, 76.1; H, 6.2. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%]. *syn* Diastereoisomer *[5RS, 1'RS]-5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone*, white prisms, m.p. 74 °C; ν_{max}($CHCl_3$) 3580, 3420 (OH), 1675 (CO), 1600, 1410, 1170 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.32 (1H, ddt, J = 20.0, 7.5 2.5 Hz, H-4a), 2.56 (1H, dt, J = 7.5, 2.5 Hz, H-5), 2.68 (1H, dq, J = 20.0, 2.5 Hz, H-4b), 3.14 (1H, d, J = 3.0 Hz, OH), 5.28 (1H, dd, J = 4.5, 3.0 Hz, H-6), 6.08 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.14-7.30 (5H, m, H-aromatic), 7.66 (1H, ddd, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 29.6 (C-4), 52.2 (C-5), 71.2 (C-6), 125.3, 127.1, 128.2, 142.6 (C-aromatic), 133.9 (C-2), 166.1 (C-3), 211.0 (C-1); m/z (C.I.) 189 $(M+1)^+$; [Found: C, 76.2; H, 6.4. $C_{12}H_{12}O_2$ requires C, 76.6; H, 6.4%].

5-(1'-Hydroxy-2'-phenylethyl)cyclopent-2-enone (36).-Starting with cyclopent-2-enone (1) (0.42 cm^3, 5.0 mmol), 2-phenylethanal (0.64 cm^3, 5.5 mmol), and following the general procedure for LDA-mediated aldol reactions of cyclopent-2-enones, (reaction time 30 min), the *title compound* (36) (0.69 g, 69%) was obtained as a yellow oil after column chromatography [silica gel, petrol-EtOAc (1:1)]. G.l.c. analysis of a sample of the crude mixture gave a *syn*:*anti* diastereoisomer ratio of 16:84; ν_{max} (film) diastereomeric mixture 3430 (OH), 3060-3040, 2920, 1680 (CO), 1580 (C=C), 1490, 1340 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 2.38-2.55 (2H, m, H-4a*, H-5), 2.82-2.92 (1H, m, H-4b*), 2.81 (1H, m, H-7a), 2.97 (1H, m, H-7b), 3.96 (1H, bs, OH), 4.03 (1H, m, H-6), 6.20 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.22-7.37 (5H, m, H-aromatic), 7.74 (1H, dt, J = 6.0, 2.5 Hz, H-3), *syn* isomer 2.40 (1H, m, H-4a*), 2.64-2.76 (2H, m, H-4b* , H-5*), 2.82 (2H, m, H-7a, H-7b), 4.43 (1H, m, H-6), 6.20 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.19-7.35 (5H, m, H-aromatic), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer

*Assignment may be interchanged.

32.9 (C-4), 41.3 (C-7), 48.5 (C-5), 73.1 (C-6), 126.5, 128.4, 129.7, 137.8 (C-aromatic), 134.0 (C-2), 164.9 (C-3), 212.8 (C-1), *syn* isomer 32.0 (C-4), 42.0 (C-7), 49.7 (C-5), 71.2 (C-6), 126.7 128.6, 129.7, 137.8 (C-aromatic), 134.3 (C-2), 165.3 (C-3), 211.3 (C-1); m/z (C.I.) 203 $(M+1)^+$, 185 $(M+1 - H_2O)^+$, 121, 83; [Found: C, 76.9; H,7.0. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%].

5-(1'-Hydroxyethyl)cyclopent-2-enone (37).-Starting with cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol) and ethanal (0.62 cm^3, 11.0 mmol) and following the general procedure for LDA-mediated aldol reactions of (1), (reaction time 30 min), the *title compound* (37) (0.79 g, 63%) was obtained as a yellow oil after column chromatography [silica gel, $CHCl_3$-MeOH, (30:1)]. G.l.c. analysis of a sample of the crude mixture gave a *syn:anti* diastereoisomer ratio of 32:68; ν_{max} ($CHCl_3$) diastereomeric mixture 3460 (OH), 2900, 1675 (CO), 1590 (C=C), 1365, 940 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.20 (3H, d, J = 6.5 Hz, H-7), 2.34-2.48 (2H, m, H-4b, H-5), 2.78-2.98 1H, m, H-4a), 3.88 (1H, dq, J = 9.5, 6.5 Hz, H-6), 4.32 (1H, bs, OH), 6.20 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3), *syn* isomer 1.25 (3H, d, J = 6.5 Hz, H-7), 2.42 (1H, m, H-4 or H-5), 2.70-2.80 (2H, m, H-4, H-5), 4.30 (1H, bs, OH), 4.32 (1H, m, H-6), 6.21 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.84 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 21.0 (C-7), 32.4 (C-4), 50.8 (C-5), 68.5 (C-6), 133.8 (C-2), 165.2 (C-3), 213.2 (C-1), *syn* isomer 21.0 (C-7), 30.4 (C-4), 51.5 (C-5), 66.4 (C-6), 134.3 (C-2), 165.8 (C-3), 211.9 (C-1); m/z (E.I.) diastereomeric mixture 126 $(M)^+$, 111 $(M-Me)^+$, 108 $(M-H_2O)^+$, 82, 45; [Found: C, 66.3; H, 8.0. $C_7H_{10}O_2$ requires C, 66.6; H, 8.0%].

5-(1'-Hydroxypropyl)cyclopent-2-enone (46).-Starting with cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol), propanal (0.72 cm^3, 10.0 mmol) and following the general procedure for LDA-mediated aldol reactions, (reaction time 50 min), the *title compound* (46) was obtained as a yellow oil after column chromatography [silica gel, petrol-EtOAc (1:2)]. G.l.c. analysis of a sample of the crude mixture gave a *syn:anti* diastereoisomer ratio of 24:76; ν_{max} (film) diastereomeric mixture 3460 (OH), 2960, 2920, 1680 (CO), 1585 (C=C), 1430 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 0.98 (3H, t, J = 7.0 Hz, H-8), 1.38-1.90 (2H, m, H-7a, H-7b), 2.50 (1H, dq, J = 18.5, 2.5 Hz, H-4a), 2.70 (1H, m, H-5), 2.94 (1H, ddt, J = 18.5, 7.0, 2.5 Hz, H-4b), 3.70 (1H, ddd, J = 10.5, 4.5, 2.0 Hz, H-6), 4.20 (1H, bs, OH),

6.20 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3), *syn* isomer 1.04 (3H, t, J = 7.0 Hz, H-8), 1.40-1.90 (2H, m, H-7a, H-7b), 2.40 (1H, m, H-4a*), 2.68-2.80 (2H, m, H-4b*, H-5*), 3.32 (1H, s, OH), 4.22 (1H, m, H-6), 6.25 (1H, dt, J = 6.0, 2.0 Hz), 7.79 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 9.1 (C-8), 27.2 (C-7), 32.1 (C-4), 48.9 (C-5), 72.8 (C-6), 133.4 (C-4), 164.8 (C-3), 212.8 (C-1), *syn* isomer 9.3 (C-8), 28.0 (C-7), 30.3 (C-4), 49.8 (C-5), 71.1 (C-6), 133.8 (C-2), 165.3 (C-3), 211.9 (C-1); m/z (E.I.) diastereomeric mixture 140 $(M)^+$, 122 $(m-H_2O)^+$, 111 $(m-C_2H_5)^+$, 82.

5-(1'-Hydroxyhexyl)cyclopent-2-enone (47).-Starting with cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol), hexanal (1.44 cm^3, 11.0 mmol) and following the general procedure for LDA-mediated aldol reactions of (1), (reaction time 55 min), the *title compound* (47) (1.14 g, 73%) was obtained as a pale-yellow oil after column chromatography [silica gel, petrol-EtOAc, (2:3)]. G.l.c. analysis of a sample of the crude mixture gave a *syn:anti* diastereoisomer ratio of 17:83; ν_{max} (film) diastereomeric mixture 3450 (OH), 2940, 2850, 1675 (CO), 1580 (C=C) cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 0.88 (3H, bt, J = 7.0 Hz, H-11), 1.22-1.34 (6H, bs, virtual coupling, H-8, H-9, H-10), 1.50 (2H, m, H-7a, H-7b), 2.34-2.46 (2H, m, H-4a, H-5), 2.85 (1H, bm, J = 18.0 Hz, H-4b), 3.72 (1H, m, H-6), 4.22 (1H, bs, OH), 6.20 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.76 (1H, dt, J = 6.0, 2.5 Hz, H-3), *syn* isomer, 0.88 (3H, bm, J = 7.0 Hz, H-11), 1.22-1.34 (6H, bs, H-8, H-9, H-10), 2.42 (1H, m, H-4 or H-5), 2.70-2.78 (2H, m, H-4 or H-5), 4.18 (1H, m, H-6), 6.16 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.80 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 13.9 (C-11), 22.5 (C-10), 24.6 (C-9), 31.7 (C-8), 35.2 (C-7), 32.5 (C-4), 49.4 (C-5), 72.1 (C-6), 133.7 (C-2), 164.8 (C-3), 213.4 (C-1), *syn* isomer, as above, except 30.2 (C-4), 50.4 (C-5), 70.1 (C-6), 134.2 (C-2), 165.4 (C-3), 211.6 (C-1); m/z (E.I.) diastereomeric mixture no $(M)^+\cdot$, 164 $(M-H_2O)^+$, 82, (C.I.) 183 $(M+1)^+$; [Found: C, 72.1; H, 10.2. $C_{11}H_{18}O_2$ requires C, 72.5, H, 10.0%].

5-(1'-Hydroxyundecyl)cyclopent-2-enone (48).-Starting with cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol), undecanal (2.27 cm^3, 11.0 mmol) and following the general procedure for LDA mediated reactions of cyclopent-2-enones, (reaction time 55 min), the *title compound* (48) (1.90 g, 72%)

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*Assignment may be interchanged.

was obtained as a yellow oil after column chromatography [silica gel, petrol-EtOAc (3:1)]. G.l.c. analysis of a sample of the crude mixture gave a *syn*:*anti* diastereoisomer ratio of 19:81. A sample of the diastereomeric mixture was separated into its *syn* and *anti* isomers by flash chromatography [silica gel, petrol-EtOAc (4:1 → 1:2)]. *anti* Diastereoisomer *[5RS,1'RS]-5-(1'-hydroxyundecyl)cyclopent-2-enone*, colourless oil, ν_{max} (film) 3470 (OH), 2920, 2850, 1680 (CO), 1580 (C=C), 1350 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, bt, J = 7.0 Hz, H-16), 1.22-1.34 (16H, bs, virtual coupling, H-8→H-15), 1.50 (2H, m, H-7), 2.34-2.46 (2H, bm, H-4a, H-5), 2.84 (1H, ddt, J = 19.0, 7.5, 2.5 Hz, H-4b), 3.70 (1H, m, H-6), 4.20 (1H, bs, OH), 6.20 (2H, dt, J = 6.0, 2.0 Hz, H-2), 7.76 (1H, dt, J = 6.0, 2.0 Hz, H-3); δ_C ($CDCl_3$) 14.1 (C-16), 22.6 (C-15), 25.0 (C-14), 29.3 (C-13), 29.5 (C-10, C-11, C-12), 29.6 (C-9), 31.9 (C-8), 32.6 (C-4), 35.5 (C-7), 49.4 (C-5), 72.2 (C-6), 133.8 (C-2), 164.7 (C-3), 213.5 (C-1); m/z (E.I.) no $(M)^+$, 234 $(M-H_2O)^+$, 111, 82 (C.I.) 253 $(M+1)^+$; [Found: C, 76.0; H, 11.5. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%]. *syn* Diastereoisomer *[5RS-1'-SR]-5-(1'-hydroxyundecyl)cyclopent-2-enone*, white waxy solid [recrystallise, petrol-ether (1:1), m.p. 53 °C]; ν_{max} ($CHCl_3$) 3600, 3480 (OH), 2900, 2840, 1680 (CO), 1580 (C=C), 1340, 1240 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, bt, J = 7.0 Hz, H-16), 1.22-1.34 (16H, bs, virtual coupling, H-8 → H-15), 1.48 (2H, m, H-7), 1.90 (1H, bs, OH), 2.42 (1H, m, H-4 or H-5), 2.68-2.78 (2H, bm, H-4, H-5), 4.16 (1H, td, J = 5.5, 3.5 Hz, H-6), 6.18 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 14.1 (C-16), 22.7 (C-15), 26.1 (C-14), 29.4 (C-13), 29.6 (C-9, C-10, C-11, C-12), 30.1 (C-4), 31.9 (C-8), 35.1 (C-7), 50.4 (C-5), 70.2 (C-6), 134.4 (C-2), 165.7 (C-3), 112.2 (C-1); m/z (C.I.) 253 $(M+1)^+$; [Found: C, 75.8; H, 11.1. $C_{16}H_{28}O_2$ requires C, 76.1; H, 11.2%].

5-(1'-Hydroxy-2'-methylpropyl)cyclopent-2-enone (49).-Starting with cyclopent-2-enone (1), (0.84 cm^3, 10.0 mmol), 2-methylpropanal (1.00 cm^3, 11.0 mmol) and following the general procedure for LDA-mediated aldol reactions of cyclopent-2-enones, (reaction time 40 min), the *title compound* (49) (1.23 g, 80%), was obtained as a yellow oil after purification by medium pressure chromatography [silica gel, petrol-EtOAc (1:1)]. G.l.c. analysis of the product showed it to be a pair of diastereoisomers having a *syn*:*anti* ratio of 6:94. Only the *anti* diastereoisomer was characterised. ν_{max} ($CHCl_3$) 3460 (OH), 2940, 2860, 1680 (CO), 1585 (C=C), 1410, 1240,

830 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, d, J= 7.0 Hz, Me), 1.02 (3H, d, J = 7.0 Hz, Me), 1.72 (1H, septet of d, J= 7.0, 3.0 Hz, H-7), 2.40 (1H, dq, J= 20.0, 2.5 Hz, H-4b), 2.48 (1H, ddd, J = 9.5, 7.5, 2.5 Hz, H-5), 2.84 (1H, ddt, J = 20.0, 7.5, 2.0 Hz, H-4b), 3.50 (1H, dd, J = 9.5, 3.0 Hz, H-6), 6.18 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 15.2 (Me), 19.8 (Me), 31.6 (C-7), 32.7 (C-4), 47.4 (C-5), 76.3 (C-6), 133.8 (C-2), 164.8 (C-3), 214.2 (C-1); m/z (C.I.) 155 $(M+1)^+$, 137 $(M+1-H_2O)^+$, 83, 73.

5-(1'-Hydroxy-2',2'-dimethylpropyl)cyclopent-2-enone (50).-Starting with cyclopent-2-enone (1) (0.42 cm^3, 5.0 mmol), 2,2-dimethylpropanal (0.62 cm^3, 5.8 mmol) and following the general procedure for LDA-mediated aldol reactions of cyclopent-2-enones, (reaction time 35 min), the *title compound* (50) (0.70 g, 83%) was obtained as an orange oil after column chromatography [silica gel, petrol-EtOAc (2:1)]. G.l.c. analysis of a sample of the crude mixture showed it to be a pair of diastereoisomers having a *syn:anti* ratio of 2:98. Only the *anti* diastereoisomer was characterised; ν_{max} (CCl_4) 3420 (OH), 2940, 1670 (CO), 1580 (C=C) cm^{-1}; δ_H ($CDCl_3$) 0.98 (9H, s, *t*-Bu), 2.24 (1H, ddd, J = 9.5, 7.5, 2.5 Hz, H-5), 2.56 (1H, dq, J = 18.0, 2.5 Hz, H-4a), 2.90 (1H, ddt, J = 18.0, 7.5, 2.5 Hz, H-4b), 3.44 (1H, d, J = 9.5 Hz, H-6), 5.20 (1H, bs, OH), 6.22 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.78 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 26.1 (C-8, C-9, C-10), 26.9 (C-7), 35.8 (C-4), 45.7 (C-5), 79.9 (C-6), 133.3 (C-2), 165.1 (C-3), 214.6 (C-1); m/z (C.I.) 169 $(M+1)^+$, 151 $(M+1-H_2O)^+$, 111, 87, 83; [Found: C, 70.6; H,9.1. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%].

General Procedure for Hydrogenation Reactions on 5-Substituted Cyclopent-2-enone Aldols

The preparation of 2-(1'-hydroxy-1'-phenylmethyl)cyclopentanone (38) is given as an example of the general experimental procedure used for a hydrogenation reaction on a 5-substituted cyclopent-2-enone aldol.

2-(1'-Hydroxy-1'-phenylmethyl)cyclopentanone (38).-To a solution of aldol (35) (64:36 diastereomeric mixture) (142 mg, 0.8 mmol) in EtOAc (15 cm^3) was added 10% palladium on carbon catalyst (13 mg). The resultant suspension was stirred at RT for 3 h under one atmosphere of hydrogen. The catalyst was then removed by filtration through a short plug of celite and

the filtrate concentrated under reduced pressure to give the title compound (38) (136 mg, 95%) as a pale-yellow oil; ν_{max} ($CHCl_3$) diasteromeric mixture 3450 (OH), 2960, 2860, 1720 (CO), 1600, 1020, 700 cm^{-1}; δ_H ($CDCl_3$) major isomer 1.28-2.54 (7H, H-alicyclic), 4.59 (1H, s, OH), 4.69 (1H, d, J = 9.0 Hz, H-6), 7.18-7.33 (5H, m, H-aromatic), minor isomer, 1.14-2.44 (7H, H-alicyclic), 3.32 (1H, s, OH), 5.26 (1H, d, J = 2.5 Hz, H-6), 7.18-7.33 (5H, m, H-aromatic); δ_C ($CDCl_3$) major isomer, 20.3 (C-4), 26.5 (C-3), 39.0 (C-5), 56.0 (C-2), 70.9 (C-6), 125.3 126.8, 128.0, 142.9 (C-aromatic), 220.5 (C-1), minor isomer 20.2 (C-4), 26.5 (C-3), 38.5 (C-5), 55.1 (C-2), 74.7 (C-6), 126.5, 127.6, 128.1, 141.2 (C-aromatic), 228.1 (C-1); m/z (E.I.) diasteromeric mixture 190 $(M)^{\ddagger}$, 172 $(M-H_2O)^{\ddagger}$, 107, 84, 77; [Found: $(M)^{\ddagger}$, 190.0991. Calc. for $C_{12}H_{14}O_2$, $(M)^{\ddagger}$, 190.0093]. Comparison of spectral data of the major and minor diastereoisomer of (38) with literature data on the *syn* and *anti* isomers of 2-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone[10a] indicated that the major diastereoisomer of (38) has *anti* relative stereochemistry (see Table 7 in Section 2.2.2).

2-(1'-Hydroxy-2'-phenylethyl)cyclopentanone (39).-Starting with aldol (36) (0.31 g, 1.5 mmol) (71:29 diastereomeric mixture) and following the general procedure for hydrogenation of 5-substituted cyclopent-2-enone aldols, (reaction time, 2 h), the title compound (39) (0.30 g, 98%) was obtained as a yellow oil. Comparison of the ^1H n.m.r. spectral data of the major and minor isomers of (39) with literature ^1H n.m.r. data on the *syn* and *anti* isomers of 2-(1'-hydroxy-2'-phenylethyl)cyclopentanone[10b] indicated the major isomer of (39) has *anti* relative stereochemistry (see Table 7 in Section 2.2.1); ν_{max} (film) diastereomeric mixture 3450 (OH), 3020, 2940, 1710 (CO), 1600, 1150, 690 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.56-2.92 (10H, H-aliphatic and OH), 3.90 (1H, m, H-6), 7.15-7.32 (5H, m, H-aromatic), *syn* isomer 1.56-2.92 (10H, H-aliphatic and OH), 4.32 (1H, t, J = 8.0 Hz, H-6), 7.15-7.32 (5H, m, H-aromatic); δ_C ($CDCl_3$) *anti* isomer 20.3 (C-4), 26.6 (C-3), 38.5 (C-5), 41.0 (C-7), 52.6 (C-2), 72.9 (C-6), 126.3, 128.1, 129.4, 137.8 (C-aromatic), 223.0 (C-1), *syn* isomer 20.4 (C-4), 22.5 (C-3), 38.3 (C-5), 41.6 (C-7), 53.2 (C-2), 70.4 (C-6), 126.1, 128.3, 129.0, 137.9 (C-aromatic), 221.9 (C-1); m/z (C.I.) diastereomeric mixture 205 $(M+1)^+$, 186 $(M-H_2O)^+$, 113, 91; (E.I.) no $(M)^{\ddagger}$, 186 $(M-H_2O)^{\ddagger}$; [Found: $(M-H_2O)^{\ddagger}$, 186.1034. Calc. for $C_{13}H_{14}O$, $(M-H_2O)^{\ddagger}$, 186.1044].

2-(1'-Hydroxyethyl)cyclopentanone (40).-Starting with aldol (37) (250 mg, 2.0 mmol) (60:40 mixture of diastereoisomers) and following the

general procedure for hydrogenation of 5-substituted cyclopent-2-enone aldols, (reaction time 4 h), the title compound (40) (243 mg, 91%) was obtained as a pale-yellow oil. Comparison of the ^{1}H n.m.r. data of the major and minor isomers of (40) with literature data for the *syn* and *anti* isomers of 2-(1'-hydroxyethyl)cyclopentanone[4b] showed that the major isomer of (40) has *anti* relative stereochemistry (Table 7, Section 2.2.2); ν_{max} ($CHCl_3$) diastereomeric mixture 3450 (OH), 2900, 2840, 1695 (CO), 840 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.18 (3H, d, J = 6.5 Hz, Me), 1.40-2.80 (7H, m, H-alicyclic), 3.85 (1H, dq, J = 9.5, 6.5 Hz, H-6), 4.10 (1H, s, OH), *syn* isomer 1.22 (3H, d, J = 6.5 Hz, Me), 1.40-2.80 (8H, m, H-alicyclic and OH), 4.26 (1H, qd, J = 6.5, 3.0 Hz, H-6); δ_C ($CDCl_3$) *anti* isomer 21.0 (C-7), 23.3 (C-4), 26.5 (C-3), 39.1 (C-5), 55.4 (C-2), 68.5 (C-6), 222.6 (C-1), *syn* isomer 20.4 (C-7), 23.3 (C-4), 26.3 (C-3), 38.3 (C-5), 55.1 (C-2), 65.8 (C-6), 222.6 (C-1); m/z (E.I.) diastereomeric mixture 128 $(M)^+$, 110 $(M-H_2O)^+$, 83, 45; [Found: $(M)^+$, 128.0817. Calc. for $C_7H_{12}O_2$, $(M)^+$, 128.0837].

2-(1'-Hydroxyundecyl)cyclopentanone (58).-Starting with aldol (48) (452 mg, 1.8 mmol) (single diastereoisomer having *anti* stereochemistry) and following the general procedure for hydrogenation of cyclopent-2-enone aldols, (reaction time 2.5 h), the *title compound* (58) (420 mg, 93%) was obtained as a yellow oil; ν_{max} (film) 3510 (OH), 2920, 1720 (CO), 1070 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 0.88 (3H, t, J = 7.0 Hz, H-16), 1.26 (16H, virtual coupling, H-8→H-15), 1.38-1.63 (4H, m, H-aliphatic), 1.79 (1H, m, H-alicyclic), 1.98-2.46 (4H, m, H-alicyclic), 3.68 (1H, m, H-6), 4.10 (1H, s, OH); δ_C ($CDCl_3$) *anti* isomer 14.1 (C-16), 20.5 (C-4), 22.6 (C-15), 24.7 (C-14), 29.8 (C-13), 29.5 (C-10, C-11, C-12), 29.6 (C-9), 31.9 (C-8), 35.1 (C-7), 38.4 (C-5), 53.8 (C-2), 72.1 (C-6), 223.9 (C-1); m/z (C.I.) 255 $(M+1)^+$, 237 $(M+1-H_2O)^+$, 84; (E.I.) no $(M)^+$, 236 $(M-H_2O)^+$; [Found: $(M-H_2O)^+$, 236.2140. $C_{16}H_{28}O$ requires $(M-H_2O)^+$, 236.2139].

Formation of Silyl Dienolates from Cyclopent-2-enones

Cross-conjugated and fully conjugated silyl dienolates of cyclopent-2-enone (1) have been prepared under kinetic and thermodynamic conditions by the methods outlined below.

Preparation of 2-(trimethylsiloxy)cyclopenta-1,3-diene (41) and 1-(trimethylsiloxy)cyclopenta-1,3-diene (42).-1. LDA-mediated enolisation (kinetic conditions).

To a stirred solution of dry distilled di-isopropylamine (1.45 cm^3, 11.0 mmol) in dry THF (15 cm^3) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium (11.0 mmol). After 10 min, the solution was cooled to -78 °C and cyclopent-2-enone (1) (0.84 cm^3, 10.0 mmol) in dry THF (5 cm^3) was added dropwise with stirring. The solution was kept at -78 °C for *ca.* 40 min, then quenched with trimethylsilyl chloride (1.40 cm^3, 11.0 mmol) and left to warm up to RT (*ca.* 40 min). The reaction mixture wad diluted with pentane (100 cm^3) and washed with saturated brine (2 x 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and carefully concentrated *in vacuo* (no heat) to leave an orange liquid. Distillation of the crude lqiuid under reduced pressure gave a colourless sweet-smelling liquid, which had a b.p. range of 36-39 °C at 14-15 mmHg. Analysis of the colourless liquid by n.m.r. spectroscopy showed it to be a mixture of *2-(trimethylsiloxy)cyclopenta-1,3-diene* (41) as the major component and *1-(trimethylsiloxy)cyclopenta-1,3-diene* (42) as the minor component. The above reaction was repeated several times with the yields of the purified mixture varying from 60-80% and regioisomer ratios of (41):(42) varying from 80:20 to 90:10. The regioisomer ratios of (41):(42) were determined by n.m.r. spectroscopy. Attempts to separate (41) and (42) by distillation and chromatography resulted in mixtures of (41), (42), starting material (1) and uncharacterised silyl products.

Spectral data for the mixture: ν_{max} (film) 3060, 2940, 2880, 1630, 1580, 1520, 870, 840 cm^{-1}; m/z (E.I.) 154 $(M)^{+}$, 82 $(C_5H_6O)^{+\cdot}$. The n.m.r. data were separated as follows: *2-(trimethylsiloxy)cyclopenta-1,3-diene* (41): δ_H ($CDCl_3$) 0.01 (9H, s, Me_3Si), 2.97 (2H, td, J = 2.0, 1.5 Hz, H-5), 5.28 (1H, p, J = 2.0 Hz, H-1), 6.30 (1H, dq, J = 5.5, 2.0 Hz, H-4), 6.41 (1H, ddt, J = 5.5, 2.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) -0.1 (C-Si), 37.8 (C-5), 104.1 (C-1), 131.9 (C-3), 133.7 (C-4), 156.4 (C-2). *1-(Trimethylsiloxy)-cyclopenta-1,3-diene* (42): δ_H ($CDCl_3$) 0.01 (9H, s, Me_3Si), 2.90 (2H, td, J = 2.0, 1.5 Hz, H-5), 5.41 (1H, dq, J = 3.0, 1.5 Hz, H-2), 5.73 (1H, dq, J = 5.5, 1.5 Hz, H-4), 6.33 (1H, dtd, J = 5.5, 2.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) -0.2 (C-Si), 41.0 (C-5), 106.2 (C-2), 120.0 (C-4), 131.8 (C-3), 161.9 (C-1).

2. Triethylamine-mediated enolisation (thermodynamic conditions)

To a precooled 0 → -20 °C mixture of triethylamine (3.48 cm^3, 25.0 mmol) and trimethylsilyl chloride (2.80 cm^3, 22.0 mmol) in dry distilled DMF (15 cm^3) under a nitrogen atmosphere was added dropwise with stirring cyclopent-2-enone (1) (1.64 cm^3, 20.0 mmol). The reaction mixture was stirred at RT for 20 h (overnight), diluted with pentane (150 cm^3) and any insoluble salts were removed by filtration. The pentane filtrate was washed with water (2 x 40 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* (no heat) to leave a yellow coloured liquid. The liquid was purified by distillation and gave a colourless sweet-smelling liquid (1.35 g, 44%) (b.p. range 37-40 °C at 14-15 mmHg). ^1H n.m.r. and ^{13}C n.m.r. analysis of the liquid showed that it consisted of 60:40 mixture of *2-(trimethylsiloxy)cyclopenta-1,3-diene* (41) and *1-(trimethylsiloxy)-cyclopenta-1,3-diene* (42). Spectral data on the products were commensurate with earlier data reported for silyl dienolates (41) and (42).

Preparation of 2-(t-butyldimethylsiloxy)cyclopenta-1,3-diene (43) *and 1-(t-butyldimethylsiloxy)cyclopenta-1,3-diene* (44).-1. LDA-mediated enolisation (kinetic conditions).

Following the same experimental procedure as that described for the LDA-mediated preparation of (41) and (42) and employing cyclopent-2-enone (0.84 cm^3, 10.0 mmol), *t*-butyldimethylsilyl chloride (1.64 g, 11.0 mmol) and HMPA as an ionising reagent (1.80 cm^3); the crude product was obtained as an orange liquid after work-up as before. The crude product was purified by either (a) passing through a short column of neutral alumina with pentane as eluant, or (b) distillation under reduced pressure (b.p. range 72-75 °C at 14-15 mmHg). Both methods of purification gave the product as a pale-yellow coloured liquid in typically 70% yield. Spectroscopic analysis of the yellow liquid showed it to be a 80:20 mixture of *2-(t-butyldimethylsiloxy)cyclopenta-1,3-diene* (43) and *1-(t-butyldimethylsiloxy)cyclopenta-1,3-diene* (44). Spectral data for the mixture: ν_{max} (film) 3080, 2960, 2840, 1630, 1600, 1520, 1350, 830 cm^{-1}; m/z (low E.I.) 196 $(M)^+$, 188 $(M-Me)^+$, 155, 140, 82 $(C_5H_6O)^+$, 75. The n.m.r. data were separated as follows:-

2-(t-butyldimethylsiloxy)cyclopenta-1,3-diene (43): δ_H ($CDCl_3$) 0.22 (6H, s, Me_2Si), 0.98 (9H, s, *t*-Bu), 2.93 (2H, td, J = 2.0, 1.5 Hz, H-5), 5.26

(1H, p. J = 2.0 Hz, H-1), 6.28 (1H, dq, J = 5.5, 2.0 Hz, H-4), 6.38 (1H, ddt, J = 5.5, 2.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) 25.6 (*t*-Bu), 37.6 (C-5), 104.4 (C-1), 132.1 (C-3), 133.4 (C-4), 156.6 (C-2).

1-(t-butyldimethylsiloxy)cyclopenta-1,3-diene (44): δ_H ($CDCl_3$) 0.22 (6H, s, Me_2Si), 0.96 (9H, *t*-Bu), 2.88 (2H, td, J = 2.0, 1.5 Hz, H-5), 5.39 (1H, dq, J = 2.0, 1.5 Hz, H-2), 5.71 (1H, dq, J = 5.5, 1.5 Hz, H-4), 6.32 (1H, dtd, J = 5.5, 2.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) 25.6 (*t*-Bu), 41.0 (C-5), 106.3 (C-2), 120.1 (C-4), 131.9 (C-3), 162.2 (C-1).

A ^1H n.m.r. decoupling experiment, irradiating at the signal centred at δ 2.93 [H-5 of (44)] simplified the spectrum of (44) as follows:- δ_H ($CDCl_3$) 0.22 (6H, s, Me_2Si), 0.98 (9H, s, *t*-Bu), 5.26 (1H, t, J = 2.0 Hz, H-1), 6.28 (1H, dd, J = 5.5, 2.0 Hz, H-4), 6.38 (1H, dd, J = 5.5, 2.0 Hz, H-3).

The above enolisation reaction was repeated under slightly different kinetic conditions, as described below:-

(a) Same conditions except HMPA was replaced by one equivalent of the less carcinogenic ionising solvent *N,N*-dimethylpropylene urea (DMPU). A similar yield (*ca.* 60%) and regioisomer ratio was obtained [(43):(44) = 75:25].

(b) Same conditions except HMPA or DMPU were omitted from the reaction. Only small amounts of the silyl dienolates were detected by t.l.c. analysis of crude reaction mixture. The reaction was not worked up.

2. Triethylamine-mediated enolisation (thermodynamic conditions)

Following the experimental procedure described for the triethylamine-mediated preparation of (41) and (42) and starting with cyclopent-2-enone (1) (2.66 cm^3, 32.0 mmol), triethylamine (4.90 cm^3, 35.0 mmol) and *t*-butyldimethylsilyl chloride (4.80 g, 32.0 mmol) in distilled DMF (20 cm^3) (reaction time 18 h), the crude product was obtained as a yellow syrup after work-up as before. The syrup was purified by distillation, furnishing a pale-yellow lqiuid (2.80 g) (b.p. 45-60 °C at 15 mmHg). ^1H N.m.r. and ^{13}C n.m.r. analyses of the liquid showed it to be a mixture of *2-(t-butyldimethylsiloxy)cyclopenta-1,3-diene* (43), *1-(t-butyldimethylsiloxy)cyclopenta-1,3-diene* (44) and cyclopent-2-enone (1) in 44:23:33 ratio.

The yield of (43) and (44) corrected for recovered (1) was 45%. Regioisomer ratio (43):(44) = 66:34.

4-Methyl-2-(trimethylsiloxy)cyclopenta-1,3-diene (45).-Following the same experimental procedure as used in the LDA-mediated preparation of enolsilanes (41) and (42), and starting with 3-methylcyclopent-2-enone (21) (2.00 cm^3, 20.0 mmol) and distilled trimethylsilyl chloride (2.00 cm^3, 22.0 mmol), the crude reaction product was obtained as a pale-orange liquid (3.10 g, 92%) after work-up as before. ^1H n.m.r. analysis of the liquid showed it to be *4-methyl-2(trimethylsiloxy)cyclopenta-1,3-diene* (45) contaminated with a small amount of unreacted 3-methylcyclopent-2-enone. No fully conjugated silyl dienolate could be detected. ν_{max} (film) 3060, 2960, 2850, 1630, 1580, 1250, 820 cm^{-1}; δ_H ($CDCl_3$) 0.20 (9H, s, Me_3Si), 1.98 (3H, d, J = 1.5 Hz, Me), 2.76 (2H, dd, J = 2.0, 1.0 Hz, H-5), 4.98 (1H, q, J = 2.0 Hz, H-1), 5.83 (1H, m, J = 2.0, 1.5, 1.0 Hz, H-3); δ_C ($CDCl_3$) 16.5 (Me), 41.0 (C-5), 101.4 (C-1), 126.8 (C-3), 145.3 (C-4), 155.8 (C-2); m/z (C.I.) 169 $(M+1)^+$, 153 $(M-Me)^+$, 97, 73 $(C_3H_9Si)^+$.

General Procedure for Aldol Reactions between 2-(Trialkylsiloxy)cyclopenta-1,3-dienes and Prochiral Aldehydes

The preparation of 5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone (35) is given as an example to demonstrate the general procedure for aldol reactions between 2-(trialkylsiloxy)cyclopenta-1,3-dienes and prochiral aldehydes mediated by Lewis acids or fluoride ion.

Reaction mediated by titanium tetrachloride.-To a standard solution of 2-(trimethylsiloxy)cyclopenta-1,3-deiene (41) (5.0 mmol of 0.94 M solution in DCM) (>90% pure) and benzaldehyde (0.58 g, 5.5 mmol) in DCM (20 cm^3) was added $TiCl_4$ (5.5 mmol) at -78 °C under a nitrogen atmosphere. The reaction mixture was stirred at -78 °C for 60 min, then quenched with 2 N hydrochloric acid (2 cm^3) and left to warm up to ambient temperature. The reaction mixture was diluted with DCM (20 cm^3) and washed with saturated brine (2 x 20 cm^3) and water (2 x 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. The oil was purified by chromatography [silica gel, petrol-EtOAc (1:1)] and afforded *5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone* (35) as a pale-yellow oil. The g.l.c. yield of (35) was 44% and the ratio of *syn*:*anti* diastereoisomers was 18:87. Spectral data of the products were identical to previously quoted data for compound (35).

Reaction mediated by tetra-*n*-butylammonium fluoride (TBAF).-To a standard solution of (41) (2.0 mmol of 0.94 M solution in DCM) (>90% pure) and benzaldehyde (0.21 g, 2.0 mmol) in DCM (5 cm^3) was added TBAF (2.40 cm^3 of a 1 M solution in THF). The reaction mixture was stirred at -78 °C for 60 min, then quenched with 2 N hydrochloric acid (1 cm^3) and left to warm up to ambient temperature. After work-up as before, the crude product was purified by chromatography [silica gel, petrol-EtOAc (1:1)] and afforded *5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone* (35) as a yellow oil. The g.l.c. yield of (35) was 85% and the ratio of *syn*:*anti* diastereomers was 74:26. Spectral data of the product were commensurate with earlier spectral data for compound (35).

The results of a study on the diastereoselectivity observed in (a) $TiCl_4$ mediated aldol reactions of (41) with a series of prochiral aldehydes and (b) aldol reactions between (41) and benzaldehyde mediated by different Lewis acids are cited in Tables 17 and 18 respectively, in Section 2.4.2. The aldol reaction illustrated in Schemes 52 and 53 and Tables 17 and 18 were performed using standard solutions of 2-(trimethylsiloxy)cyclopenta-1,3-diene in DCM (>90% cross-conjugated silyl dienolate). The reactions were performed on 2 mmol scale in dry DCM at -78 °C (reaction times 30 to 60 min) under a nitrogen atmosphere using 1.2 equivalents of Lewis acid. The addition reactions were performed more than once and yields and diastereoisomer ratios refer to the most typical result. Yields and diastereoisomer ratios were determined by g.l.c. analysis using an internal standard. The aldol products were identified by comparison of their spectral data with data from products obtained from the LDA-mediated aldol reactions of (1).

The same experimental procedure was used for aldol reactions involving silyl dienolate (43). Similar levels of diastereoselectivity were observed, but the yields were lower.

Aldol reaction between the zirconium dienolate of cyclopent-2-enone (1) and benzaldehyde.-To a stirred solution of di-isopropylamine (0.77 cm^3, 5.5 mmol) in freshly distilled THF (20 cm^3) at 0 °C under a nitrogen atmosphere, was added *n*-butyllithium (5.5 mmol). After 10 min, the solution was cooled to -78 °C and cyclopent-2-enone (1) (0.42 cm^3, 5.0 mmol) in dry THF (5 cm^3) was added dropwise. After stirring for

40 min, zirconocene dichloride* (1.60 g, 5.5 mmol) in THF (25 cm^3) was added. The cloudy suspension which formed was warmed to -40 °C and stirred for 1 h. The suspension was then cooled to -78 °C and benzaldehyde (0.56 cm^3, 5.5. mmol) in THF (5 cm^3) was added dropwise. The mixture was stirred for a further 80 min then quenched with saturated aqueous ammonium chloride solution (8 cm^3). A white solid immediately precipiated (zirconium salt), the mixture was warmed to room temperature, the solid was removed and washed with DCM (20 cm^3). The filtrate and DCM washings were combined and concentrated under reduced pressure to leave a cloudy yellow syrup which was partitioned between DCM (60 cm^3) and dilute hydrochloric acid (2 N $HCl:H_2O$ = 1:2, 30 cm^3). The organic layer was separated and washed with water (3 x 20 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to leave a brown oil. The oil was purified by column chromatography [silica gel, petrol-EtOAc, (2:1)] and gave *5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone* (35) (0.28 g) as a yellow oil,† together with benzaldehyde (0.24 g). The yield of (35) corrected for recovered benzaldehyde was 50%. The *syn:anti* diastereoisomer ratio of the oil was found to be 83:17, determined from its ^1H n.m.r. spectrum. The spectral data of the aldol product were identical to those previously reported for compound (35).

Aldol reaction between the zirconium dienolate of cyclopent-2-enone (1) and undecanal.-Following the same experimental procedure as described in the previous experiment and starting with cylopent-2-enone (1) (0.42 cm^3, 5.0 mmol) and undecanal (1.20 cm^3, 5.8 mmol) (reaction time after addition of aldehyde = 60 min), the crude product was obtained as an orange oil (1.20 g) after work-up as before. Purification by medium pressure column chromatography [silica gel, petrol-EtOAc (3:1)] gave *5-(1'-hydroxyundecyl)cyclopent-2-enone* (48) as a racemic mixture of *syn* (135 mg, pale-yellow solid, m.p. 53 °C) and *anti* (120 mg, colourless oil) diastereoisomers, together with unreacted undecanal (0.43 g). The yield of (48) corrected for the recovery of undecanal was 30%. The diastereoisomer ratio was *syn:anti* = 53:47, based on isolated products. Spectroscopic data for the products were commensurate with data reported earlier for compound (48).

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*Zirconocene dichloride is commercially available.

†Oil began to crystallise on prolonged storage at -20 °C.

Aldol reaction between cyclopent-2-enone (1) and benzaldehyde mediated by triethylamine (thermodynamic conditions).-To a stirred solution of cyclopent-2-enone (1) (0.42 cm^3, 5.0 mmol) and benzaldehyde (0.51 cm^3, 5.0 mmol) in methanol (5 cm^3) was added triethylamine (0.70 cm^3, 5.0 mmol). The mixture was stirred at room temperature for 24 h, then concentrated *in vacuo* to leave a brown oil. The oil was purified by column chromatography [silica gel, petrol-EtOAc (1:1)] to give two products. The major product (yellow oil) was identified as *2-(1'-hydroxy-1'-phenylmethyl)-cyclopent-2-enone* (55) (0.24 g, 25%); ν_{max} (film) 3450 (OH), 1685 (C=O) cm^{-1}; δ_H ($CDCl_3$) 2.38 (2H, m, H-5), 2.54 (2H, m, H-4), 3.85 (1H, bs, OH), 5.50 (1H, s, H-6), 7.25-7.37 (6H, m, H-aromatic and H-3); δ_C ($CDCl_3$) 26.6 (C-4), 35.2 (C-5), 69.5 (C-6), 126.3, 127.7, 128.4, 141.5 (C-aromatic), 147.8 (C-2), 159.6 (C-3), 209.6 (C-1); m/z (E.I.) 188 $(M)^+$, 170 $(M-H_2O)^+$.

The minor product, a yellow oil, was identified as *5-(1'-hydroxy-1'-phenylmethyl)cyclopent-2-enone* (35) (0.17 g, 18%) (*syn*:*anti* diastereoisomer ratio 53:47) by comparison with previous spectral data.

5-(1'-Hydroxy-1'-phenylmethyl)pentan-5-olide (57).-To an ice-cold solution of the 2-substituted cyclopentanone (38) (50 mg, 0.3 mmol) (*ca.* 60:40 = *anti*:*syn* diastereomeric mixture), in dichloromethane (3 cm^3) was added finely powdered sodium hydrogen carbonate (44 mg, 0.5 mmol) and 3-chloroperoxybenzoic acid (MCPBA) (0.4 mmol). The resulting suspension was stirred at room temperature under a nitrogen atmosphere for 3 h and then treated with 10% (w/v) solution of sodium thiosulphate (1 cm^3) to destroy any excess oxidant. After stirring for 30 min, the reaction mixture was diluted with DCM (10 cm^3), washed with saturated sodium hydrogen carbonate solution (2 x 5 cm^3) and brine (2 x 5 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to afford the *title compound* (57) (54 mg, 98%) (*ca.* 60:40 mixture of diastereoisomers) as a colourless solid, m.p. 98-104 °C; ν_{max} ($CHCl_3$) diastereomeric mixture, 3580, 3450 (OH), 2900, 2840, 1710 (CO), 1230, 1050, 850 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.50-1.92 (4H, bm, H-3, H-4), 2.39 (1H, m, J_{gem} = 18.0 Hz, H-2a), 2.55 (1H, m, J_{gem} = 18.0 Hz, H-2b), 3.42 (1H, s, OH), 4.46 (1H, dt, J = 11.0, 4.0 Hz, H-5), 5.02 (1H, d, J = 4.0 Hz, H-6), 7.24-7.41 (5H, m, H-aromatic), *syn* isomer 1.38-1.91

(4H, bm, H-3, H-4), 2.37 (1H, m, J_{gem} = 18.0 Hz, H-2a), 2.56 (1H, m, J_{gem} = 18.0 Hz, H-2b), 3.56 (1H, bs, OH), 4.38 (1H, ddd, J = 11.0, 7.0, 4.0 Hz, H-5), 4.66 (1H, d, J = 7.0 Hz, H-6), 7.27-7.40 (5H, m, H-aromatic); δ_C ($CDCl_3$) *anti* isomer 18.1 (C-3), 20.2 (C-4), 29.6 (C-2), 74.0 (C-6), 84.3 (C-5), 127.1, 127.7, 128.3, 128.7 (C-aromatic), 171.3 (C-1), *syn* isomer 18.1 (C-3), 23.8 (C-4), 29.5 (C-2), 76.5 (C-6), 84.1 (C-5), 127.0. 127.7, 128.4, 138.7 (C-aromatic), 171.3 (C-1); m/z (E.I.) diastereomeric mixture 206 $(M)^+$, 107 $(C_7H_7O$ = side chain$)^+$, (C.I.) 207 $(M+1)^+$, 189 $(M+1-H_2O)^+$, 107 (side chain)$^+$, 100; [Found: C, 69.5; H, 6.9. $C_{12}H_{14}O_3$ requires C, 69.8; H, 6.8%].

5-(1'-Hydroxyundecyl)pentan-5-olide (59).-Starting with the 2-substituted cyclopentanone (58) (0.12 g, 0.5 mmol) (*anti* stereoisomer), MCPBA (0.9 mmol), sodium hydrogen carbonate (75 mg, 0.9 mmol) and following the same experimental procedure used in preparation of lactone (57) (reaction time 3.5 h), the *title compound* (59) (117 mg, 91%) was obtained as a pale-yellow solid after work-up as before, m.p. 52-55 °C (recrystallised hexane); ν_{max} ($CHCl_3$) 3580 (OH), 2930, 2850, 1720 (CO), 1430, 1140, 1240, 1055, 850 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, t, J = 7.0 Hz, H-16), 1.26 (16H, bs, virtual coupling, H-8 → H-15), 1.53 (2H, m, H-7), 1.66-2.02 (4H, bm, H-3, H-4), 2.46 (1H, bm, J_{gem} = 17.0 Hz, H-2b), 2.62 (1H, bm, J_{gem} = 17.0 Hz, H-2a), 3.00 (1H, bs, OH), 3.57 (1H, dt, J = 6.5, 4.5 Hz, H-6), 4.20 (1H, dt, J = 10.0, 4.5 Hz, H-5); δ_C ($CDCl_3$) 14.0 (C-16), 18.3 (C-3), 22.6 (C-15), 24.0 (C-4), 25.4 (C-14), 29.2 (C-13), 29.2 (C-2), 29.5 (C-10, C-11, C-12), 29.6 (C-9), 31.8 (C-8), 32.5 (C-7), 73.2 (C-6), 83.2 (C-5), 171.6 (C-1); m/z (C.I.) 271 $(M+1)^+$, 253 $(M+1 - H_2O)^+$, 171, 100; [Found: C, 69.4; H, 10.9. $C_{16}H_{30}O_3$ requires C, 71.1; H, 11.2%].

When the spectral data of lactone (59) (single racemic diastereoisomer) was compared with published spectral data for the *anti* diastereoisomer of 5-(1'-hydroxyundecyl)pentan-5-olide,[55] the two sets of data were similar, but not identical, which suggests lactone (59) is a *syn* diastereoisomer (see Table 20 in Section 2.7.1.).

5-(1'-t-Butyldimethylsiloxy-1'-phenylmethyl)pentan-5-olide (64).-To a stirred solution of imidazole (0.93 g, 13.6 mmol) and *t*-butyldimethylsilyl chloride (1.02 g, 6.8 mmol) in dry DMF (3 cm^3) was added the hydroxy lactone (57) (1.00 g, 4.8 mmol) (2:1 *anti*:*syn* diastereoisomer mixture). The cloudy reaction mixture was warmed to 40 °C and stirred for 4 h. T.l.c. analysis of the reaction mixture indicated that there was still some unreacted starting lactone (57). An additional 0.5 equivalent of *t*-butyldimethylsilyl chloride was added and the mixture was stirred at room temperature for a further 16 h. T.l.c. analysis indicated that some starting lactone (57) was still present. The reaction mixture was diluted with DCM (20 cm^3) and washed with water (2 x 100 cm^3). The organic layers were collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow syrup. The crude product was separated from unreacted starting material by column chromatography [silica gel, petrol-EtOAc (1:1)] and furnished the *title compound* (64) (0.68 g, 44%) as a pale-yellow oil; ν_{max} ($CHCl_3$) diastereomeric mixture 3040, 2915, 2860, 1720 (CO), 1250, 1070, 830 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 0.90 (9H, s, *t*-Bu), 1.54-1.96 (4H, m, H-3, H-4), 2.16-2.61 (2H, m, H-2), 4.34 (1H, dt, J = 10.5, 3.5 Hz, H-5), 4.97 (1H, d, J = 3.5 Hz, H-6), 7.22-7.38 (5H, m, H-aromatic), *syn* isomer 0.89 (9H, s, *t*-Bu), 1.54-1.96 (4H, m, H-3, H-4), 2.16-2.61 (2H, m, H-2), 4.40 (1H, ddd, J = 10.5, 7.0, 3.5 Hz, H-5), 4.79 (1H, d, J = 7.0 Hz, H-6), 7.22-7.38 (5H, m, H-aromatic); δ_C ($CDCl_3$) *anti* isomer, 18.3 (C-3), 20.3 (C-4), 25.8 (*t*-Bu), 30.0 (C-2), 75.6 (C-6), 84.7 (C-5), 126.2, 127.6, 128.2, 140.2 (C-aromatic), 171.2 (C-1), *syn* isomer 18.2 (C-3), 22.9 (C-4), 25.8 (*t*-Bu), 29.8 (C-2), 77.0 (C-6), 83.4 (C-5), 126.7, 127.5, 128.4, 140.0 (C-aromatic), 171.2 (C-1); m/z (C.I.) diastereomeric mixture 321 $(M+1)^+$, 263 $(M-t\text{-}Bu)^+$, 221; [Found: C, 67.1; H, 8.7. $C_{18}H_{28}O_3Si$ requires C, 67.7; H, 8.8%].

Attempted preparation of 5-(1'-t-butyldimethylsiloxy-1'-phenylmethyl)-2-(phenylseleno)pentan-5-olide (65).-To an ice cold stirred solution of diisopropylamine (0.6 mmol) in distilled THF (1 cm^3) under a nitrogen atmosphere was added *n*-butyllithium (0.6 mmol). After 10 min the solution was cooled to -78 °C and lactone (64) (154 mg, 0.5 mmol) in dry THF (1 cm^3) was added dropwise. After stirring for *ca.* 40 min, diphenyldiselenide (180 mg, 0.6 mmol) in dry THF (1 cm^3) was added and the reaction mixture was left to stir at -78 → -40 °C, the progess of the reaction was monitored by t.l.c. After 1.5 h, t.l.c. indicated only

starting material to be present, no reaction was proceeding. The reaction mixture was then allowed to warm to ambient temperature and quenched with dilute hydrochloric acid (0.5 cm^3). The mixture was diluted with DCM (10 cm^3) and washed with water (2 x 3 cm^3) and brine solution (2 x 3 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated *in situ* to leave a yellow oil. Medium pressure column chromatography on the oil afforded unreacted lactone (64) and diphenyldiselenide. The reaction was repeated under different conditions:-

(1) Employing phenylselenyl chloride instead of diphenyldiselenide.

(2) Performing the reaction on lactone (57), instead of lactone (64) and using 2.2 equivalents of LDA.

Both reactions were unsuccessful, phenylselenyl residues and unreacted starting reagents were the only identifiable components after work-up.

Attempted preparation of 5-(1'-siloxy-1'-phenylmethyl)pent-2-en-5-olide (66).-An attempt was made to prepare the unsaturated lactone (66) from lactone (64) without isolating the intermediate 2-phenylselenolactone (65). Following the same experimental procedure as that described for the attempted preparation of (65) (employing diphenyl diselenide), but instead of quenching the reaction mixture with dilute hydrochloric acid, 1.1 equivalents of sodium metaperiodate in MeOH-H_2O (1:1) were added and the resulting suspension was stirred at room temperature for 1 h. Work-up as before yielded a multi component mixture which was not characterised.

2-(1'-Hydroxyhexyl)-4-(phenylthio)cyclopentanone (67).-To a solution of the *anti* diastereoisomer of aldol (47) (0.91 g, 5.0 mmol) and thiophenol (0.52 cm^3, 5.1 mmol) in chloroform (20 cm^3) at 0 °C was added with stirring triethylamine (0.10 cm^3). The reaction mixture was allowed to warm to ambient temperature and stirred for 2 h, then diluted with DCM (20 cm^3), washed with 5% w/v sodium hydroxide solution (2 x 20 cm^3) and water (2 x 20 cm^3). The organic layers were collected, dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown oil. Medium pressure column chromatography on the oil [silica gel, petrol] afforded the *title compound* (67) as a brown oil (0.78 g, 54%) mixture of two pairs of diastereoisomers in *ca.* 2:1 ratio) by ^{13}C n.m.r. analysis: ν_{max} (film)

diastereomeric mixture 3450 (OH), 3050, 1720 (CO), 1575, 1460, 1090, 730 cm^{-1}; δ_H ($CDCl_3$) diastereomeric mixture 0.88 (3H, bt, H-11), 1.28 (6H, virtual coupling H-8, H-9, H-10), 1.34-1.60 (3H, m, H-7, H-alicyclic), 2.00-2.80 (5H, bm, H-alicyclic), 3.56-4.20 (2H, m, OH, H-6), 7.18-7.50 (5H, m, H-aromatic); δ_C ($CDCl_3$) major isomer 13.9 (C-11), 22.4 (C-10), 24.6 (C-9), 31.4 (C-8), 32.0 (C-4), 33.7 (C-7), 40.3 (C-3), 45.2 (C-2), 50.4 (C-5), 72.0 (C-6), 220.0 (C-1), minor isomer 14.0 (C-11), 22.5 (C-10), 24.4 (C-9), 31.6 (C-8), 32.5 (C-4), 34.8 (C-7), 41.0 (C-3), 45.0 (C-2), 54.4 (C-5), 72.1 (C-6), 219.6 (C-1); m/z (E.I.) diastereomeric mixture 292 $(M)^+$, 274 $(M-H_2O)^+$, 218, 164, 121, 109 $(PhS)^+$, 82, 77.

5-(1'-Hydroxyhexyl)-3-(phenylsulfonyl)pentan-5-olide (68).-To a solution of cyclopentanone derivative (67) (285 mg, 1.0 mmol) in DCM (6 cm^3) at 0 °C under a nitrogen atmosphere was added (0.30 g, 1.0 mmol) of solid sodium hydrogen carbonate (buffer). The solution was stirred at 0 °C for 3 min, then a solution of MCPBA (0.60 g, 3.0 mmol) in DCM (5 cm^3) was added. The resulting suspension was stirred at room temperature and the progress of the reaction was monitored by t.l.c. [silica gel, petrol-EtOAc]. After 20 h, the reaction mixture was diluted with DCM (50 cm^3) and washed with saturated aqueous sodium hydrogen carbonate solution (2 x 15 cm^3), 1N hydrochloric acid (2 x 15 cm^3) and brine solution (15 cm^3). The organic layers were collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave a brown oil. Medium pressure column chromatography [silica gel, petrol-EtOAc (2:3)] on the oil, afforded the *title compound* (68) as a yellow oil (59 mg, 17%) (mixture of two pairs of diastereoisomers in *ca.* 60:40 ratio by n.m.r. analysis); ν_{max} ($CDCl_3$) diastereomeric mixture 3560 (OH), 2900, 2840, 1735 (CO), 1305 (SO_2), 1150 (SO_2), 1060 cm^{-1}; δ_H ($CDCl_3$) major isomer 0.88 (3H, m, H-11), 1.28 (6H, bs, H-8, H-9, H-10), 1.42-1.64 (2H, m, H-7), 2.00-2.44 (2H, m, H-4), 2.60-2.93 (2H, m, H-2), 3.04 (1H, bs, OH), 3.58 (2H, m, H-3, H-6), 4.20 (1H, dt, J = 12.0, 3.5 Hz, H-5), 7.62 (2H, td, J = 8.0, 1.0 Hz, H-3', H-5' aromatics), 7.72 (1H, tt, J = 8.0, 1.0 Hz, H-4' aromatic), 7.90 (2H, dd, J = 8.0, 1.0 Hz, H-2', H-6' aromatic), minor isomer as above except 3.04 (1H, bs, OH), 3.58 (1H, m, H-6), 3.73 (1H, m, H-3), 4.45 (1H, dt, J = 9.5, 3.5 Hz, H-5); δ_C ($CDCl_3$) major isomer 14.0 (C-11), 22.5 (C-10), 24.1 (C-9), 25.1 (C-8), 29.7 (C-4), 31.6 (C-7), 32.6 (C-2), 56.4 (C-3), 72.7 (C-6), 80.9 (C-5), 128.7, 129.0, 129.7, 135.2 (C-aromatic), 167.6 (C-1), minor isomer,

as above, except 29.3 (C-4), 33.2 (C-2), 54.4 (C-3), 72.7 (C-6), 78.9 (C-5), 128.7, 129.0, 129.7, 136.4 (C-aromatic), 168.9 (C-1); m/z (C.I.) diastereomeric mixture, 341 $(M+1)^+$, 199 $(M+1-PhSO_2H)^+$, 181, 156, 129, 98.

5-(1'-Hydroxyhexyl)pent-2-en-5-olide (69).-To a solution of lactone (68) (40 mg, 0.1 mmol) in chloroform (6 cm^3) at 0 °C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (36 mg, 0.23 mmol). The reaction mixture was stirred at 0 °C → RT for 20 h and at 40 °C for 1 h, then an additional equivalence of DBU was added and the mixture was stirred at 40 °C for a further 1 h. The reaction mixture was then diluted with chloroform (10 cm^3), washed with 1N hydrochloric acid (2 x 10 cm^3), saturated aqueous sodium hydrogen carbonate solution (2 x 10 cm^3), brine solution (10 cm^3), dried ($MgSO_4$) and concentrated *in vacuo* to give an orange oil. Purification of the crude product by medium pressure chromatography [silica gel, petrol-EtOAc (2:3)] gave the *title compound* (69) as a yellow oil (13 mg, 56%). N.m.r. spectroscopy revealed the product to be a single diastereoisomer having *syn* stereochemistry about the C_5-C_6 bond; ν_{max} (film) 3570 (OH), 2910, 2840, 1705 (CO), 1360, 1240, 1050, 810 cm^{-1}; δ_H ($CDCl_3$) 0.90 (3H, t, J = 7.0 Hz, H-11), 1.32 (4H, m, H-9, H-10), 1.58 (4H, m, H-7, H-8), 2.20 (1H, bs, OH), 2.30 (1H, dddd, J = 18.0, 6.5, 4.0, 1.0 Hz, H-4a), 2.62 (1H, ddt, J = 18.0, 13.0, 2.0 Hz, H-4b), 3.65 (1H, m, H-6), 4.35 (1H, dt, J = 13.0, 4.0 Hz, H-5), 6.04 (1H, ddd, J = 10.0, 2.0, 1.0 Hz, H-2), 6.95 (1H, ddd, J = 10.0, 6.5, 2.0 Hz, H-3); δ_C ($CDCl_3$) 14.0 (C-11), 22.6 (C-10), 25.1 (C-9), 26.0 (C-8), 31.7 (C-7), 32.6 (C-5), 72.6 (C-6), 80.5 (C-4), 121.0 (C-2), 145.5 (C-3), 163.8 (C-1); m/z (E.I.) no $(M)^+$, 98 [$M-C_6H_{13}O$= side chain)]$^+$, (C.I.) 199 $(M+1)^+$, 181 $(M+1-H_2O)^+$; [Found: $(M-C_6H_{13}O)^+$, 98.0360. $C_5H_6O_2$ requires $(M-C_6H_{13}O)^+$, 98.0367].

1,2:5,6-Di-O-isopropylidene-D-mannitol[66] (72).-Anhydrous zinc chloride (60 g), was shaken with dry acetone (600 cm^3) and the solution was vigorously stirred with *D*-mannitol (71) (10.00 g, 55.0 mmol) at room temperature for 18 h. The reaction mixutre was diluted with chloroform (250 cm^3) cooled to 0 °C and treated with an aqueous solution of potassium carbonate (70 g in 75 cm^3 of water). After the mixture had been stirred for an additional 30 min, the supernatant was separated from the resulting slurry, and the white precipitate was washed by vigorous stirring with chloroform (2 x 150 cm^3). The first supernatant

was concentrated below 40 °C to approximately 150 cm^3 and combined with the chloroform extracts. The mixture was then separated into two phases. The lower layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound (72) as a white crystalline solid (11.20 g, 77%), (recrystallised from petrol, m.p. 120 °C, lit.,[66] m.p. 120 °C); ν_{max} (Nujol), 3300 (OH), 1080, 870 cm^{-1}; δ_H ($CDCl_3$) 1.30 (6H, s, 2Me), 1.40 (6H, s, 2Me), 3.15 [2H, d, J = 7.0 Hz, 2(OH)], 3.70 (2H, t, J = 7.0, H-3, H-4), 3.90-4.25 (6H, m, H-1, H-2, H-5, H-6); δ_C ($CDCl_3$) 25.3 (2Me), 26.8 (2Me), 66.9 (C-1, C-6), 70.9 (C-3, C-4), 75.6 (C-2, C-5), 109.4 [2(>C<)]; m/z (C.I.) 263 $(M+1)^+$, 247 $(M-Me)^+$, 205, 147, 129, 101; [Found: C, 54.4; H, 8.6. Calc. for $C_{12}H_{12}O_6$ C, 54.9; H, 8.4%].

(2R)-2,3-O-isopropylideneglyceraldehyde[66] (70).-To an ice cold, vigorously stirred, solution of (72) (10.0 g, 38.0 mmol) and sodium hydrogen carbonate (3.20 g, 38.0 mmol) in dry benzene (250 cm^3) was added portionwise, finely powdered lead tetraacetate (18.00 g, 40.5 mmol). The suspension was stirred at room temperature for 1.5 h, then separated from any inorganic salts by filtration through a short plug of celite. The filtrate was carefully concentrated by use of an efficient fractionating column to leave a sweet smelling cloudy yellow liquid. The crude product, which was contaminated with traces of lead salts and acetic acid, was purified by distillation under reduced pressure to afford (2R)-2,3-O-isopropylindeneglyceraldehyde (70) as a colourless liquid (5.00 g, 51%), which boils at 40-45 °C at 13-15 mmHg, (lit.,[66] b.p. 35-42 °C at 11 mmHg). The product (70) was used immediately, as it tended to polymerise on standing at room temperature, but it could be stored in a benzene matrix at -20 °C; ν_{max} (film), 2960, 1720 (C=O), 1210, 1060, 830 cm^{-1}; δ_H ($CDCl_3$) 1.38 (3H, s, Me), 1.42 (3H, s, Me), 3.80-4.20 (3H, m, H-2, H-3a, H-3b), 9.60 (1H, d, J = 2.0 Hz, H-1); δ_C ($CDCl_3$) 25.1 (Me), 26.2 (Me), 65.4 (C-3), 80.0 (C-2), 110.0 (>C<), 201.7 (C-1).

5-(1'-Hydroxy-2',3'-isopropylidendioxypropyl(cyclopent-2-enone (73).-Starting with cyclopent-2-enone (1) (0.42 cm , 5.0 mmol), (2R)-2,3-*O*-isopropylidenglyceraldehyde (70) (0.72 g, 5.5 mmol) and following the general experimental procedure for LDA-mediated aldol reactions of cyclopent-2-eones (reaction time 60 min), the *title compound* (73) (0.61 g, 57%) was obtained as a yellow oil after the usual work-up and separation from high boiling resinous components by medium pressure column chromatography [silica gel, petrol-EtOAc]. G.l.c. analysis of a sample of the partially purified product showed that it contained predominantly

two stereoisomers in a 58:42 ratio. A sample of the partially purified oil (two stereoisomers) was separated into individual isomers by flash chromatography [silica gel, MeOH-$CHCl_3$ (4:96), R_f 0.34 and 0.32]. Each column fraction was analysed by g.l.c. and hence it was possible to obtain almost pure (>95%) samples of each stereoisomer. The aldol reaction was repeated several times, the yields and stereoisomer ratios quoted refer to the most typical result.

Major stereoisomer (pale-yellow oil); ν_{max} (film) 3450 (OH), 2980, 1680 (CO), 1580 (C=C), 1370, 1060, 840 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, Me), 1.40 (3H, s, Me), 2.51 (1H, ddd, J = 7.5, 6.0, 2.5 Hz, H-5), 2.76 (1H, dq, J = 18.0, 2.5 Hz, H-4a), 2.91 (1H, ddt, J = 18.0, 6.0, 2.5 Hz, H-4b), 3.66 (1H, bt, J = 7.5 Hz, H-6), 4.03 (1H, m, H-7*), 4.12 (2H, bm, H-8a*, H-8b*), 4.37 (1H, bs, OH), 6.22 (1H, dt, J = 6.0, 2.0 Hz, H-2), 7.80 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 25.3 (Me), 26.5 (Me), 33.0 (C-4), 47.8 (C-5), 67.1 (C-8), 73.6 (C-6), 78.3 (C-7), 109.4 (>C<), 133.5 (C-2), 165.9 (C-3), 212.9 (C-1); m/z (E.I.) no $(M)^+$, 197 $(M-Me)^+$, 194 $(M-H_2O)^+$, 111 $(C_6H_7O_2)^+$, 101 $(C_5H_9O_2)^+$, 82 $(C_6H_5O)^+$; (C.I.) 213 $(M+1)^+$; [Found: $(M-Me)^+$ 197.0799; $C_{10}H_{13}O_4$ requires $(M-Me)^+$, 197.0813]. A ^1H n.m.r. (270 MHz) spectrum of the major stereoisomer was run in deuterobenzene to see if the spectrum simplified. δ_H (C_6D_6) 1.28 (3H, s, Me), 1.33 (3H, s, Me), 2.13 (1H, m, H-5), 2.25 (1H, bm, J = 18.0 Hz, H-4b), 2.34 (1H, dq, J = 18.0, 2.5 Hz, H-4a), 3.46 (1H, bt, J = 7.5 Hz, H-6), 4.00-4.13 (3H, bm, H-7, H-8a, H-8b), 4.50 (1H, s, OH), 5.78 (1H, dt, J = 6.0, 2.0 Hz, H-2), 6.81 (1H, dt, J = 6.0, 2.5 Hz, H-3).

Homonuclear spin decoupling experiment (^1H n.m.r. 270 MHz, $CDCl_3$); When the signal centred at δ 2.51 (H-5) was irradiated, H-6 simplified from a bt (J = 7.5 Hz) to a d (J = 7.0 Hz), H-4a simplified from a dq to a dm (J = 18.0 Hz and very fine coupling) and H-4b simplified from a ddt to a dm (J = 18.0 Hz and fine coupling). The rest of the spectrum was unaffected.

Irradiation at signal centred at δ 3.66 (H-6) resulted in H-5 simplifying from a ddd to a dm (J = 6.0 Hz and fine coupling), H-7, H-8a, H-8b simplifed from a complex bm to a bm with less fine coupling. The rest of the spectrum was unaffected.

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*Assignment may be interchanged.

Minor stereoisomer (yellow oil); ν_{max} ($CHCl_3$) 3670, 3450 (OH), 2940, 1700 (CO), 1590 (C=C), 1380, 1060, 850 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, Me), 1.42 (3H, s, Me), 2.70 (1H, m, H-5), 2.75 (1H, ddt, J = 18.0, 6.0, 2.5 Hz, H-4a), 2.88 (1H, dq, J = 18.0, 2.5 Hz, H-4b), 3.36 (1H, bs, OH), [4.00 (1H, dd, J = 8.5, 5.0 Hz), 4.05 (1H, m), 4.14 (2H, m), H-6, H-7, H-8a, H-8b], 6.21 (1H, dt, J = 6.0. 2.0 Hz, H-2), 7.82 (1H, dt, J = 6.0, 2.5 Hz, H-3); δ_C ($CDCl_3$) 25.3 (Me), 26.5 (Me), 29.6 (C-4), 47.8 (C-5), 66.9 (C-8), 70.6 (C-6), 76.7 (C-7), 109.4 (>C<), 134.0 (C-2), 166.0 (C-3), 211.7 (C-1); m/z (E.I.) no $(M)^{\ddagger}$, 147 $(M-Me)^{\ddagger}$, (C.I.) 213 $(M+1)^{+}$; [Found: $(M-Me)^{\ddagger}$, 197.0795. $C_{10}H_{13}O_4$ requires $(M-Me)^{\ddagger}$, 197.0813].

5-(1'-Hydroxy-2',3'-isopropylidendioxypropyl)-3-methylcyclopent-2-enone (74).-Starting with 3-methylcyclopent-2-enone (21) (0.50 cm^3, 5.0 mmol) and (2R)-2,3-O-isopropylidenglyceraldehyde (70) (0.72 g, 5.5 mmol) and following the general experimental procedure for LDA-mediated aldol reactions of cyclopent-2-enones (reaction time 60 min), the *title compound*(74) (0.73 g, 64%) was obtained as an orange oil after the usual work-up and column chromatography [silica gel, petrol-EtOAc]. The initial chromatography was used to separate the aldol adducts from high boiling polymeric material which is produced in all aldol reactions involving cyclopent-2-enones. Samples of the partially purified oil and crude reaction product were analysed by g.l.c. Both samples contained mixtures of two stereoisomers in a 60:40 ratio. Pure samples of each stereoisomer were obtained by flash chromatography on the semi-purified oil [silica gel, MeOH-$CHCl_3$ (3:97), R_f 0.40 and 0.36].

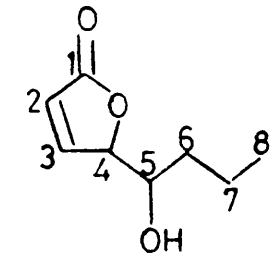
Major stereoisomer (pale-yellow oil); ν_{max} ($CHCl_3$) 3420 (OH), 2960, 1670 (CO), 1610 (C=C), 1360, 1060, 830 cm^{-1}; δ_H ($CDCl_3$) 1.36 (3H, s, Me), 1.40 (3H, s, Me), 2.17 (3H, s, Me), 2.55 (1H, m, H-5), 2.66 (1H, m, J = 18.0 Hz, H-4a), 2.77 (1H, dd, J = 18.0, 6.0 Hz, H-4b), 3.66 (1H, bt, J = 7.5 Hz, H-6), 3.90-4.17 (3H, m, H-7, H-8a, H-8b), 4.64 (1H, s, OH), 5.96 (1H, s, fine coupling, H-2); δ_C ($CDCl_3$) 19.5 (Me), 25.4 (Me), 26.5 (Me), 36.9 (C-4), 49.5 (C-5), 67.2 (C-8), 73.8 (C-6), 78.7 (C-7), 109.3 (>C<), 129.6 (C-2), 180.4 (C-3), 212.6 (C-1); m/z (E.I.) no $(M)^{\ddagger}$, 211 $(M-Me)^{\ddagger}$, 208 $(M-H_2O)^{\ddagger}$, 125, 101, 96; (C.I.) 227 $(M+1)^{+}$ [Found: $(M-Me)^{\ddagger}$, 211.0956. $C_{11}H_{15}O_4$ requires $(M-Me)^{\ddagger}$, 211.0968].

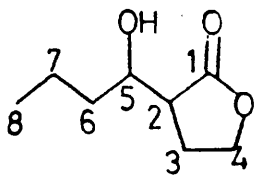
Minor stereoisomer (pale-yellow oil); ν_{max} ($CHCl_3$) 3580,3400 (OH), 2960, 2880, 1670 (CO), 1610 (C=C), 1370, 10801 850 cm^{-1}; δ_H ($CDCl_3$) 1.35 (3H, s, Me), 1.42 (3H, s, Me), 2.17 (3H, s, Me), 2.61 (1H, dm, J = 18.0, 7.5 Hz, H-4a), 2.72-2.82 (2H, m, H-4b, H-5), 3.08 (1H, bs, OH), 3.94-4.18 (4H, m, H-6, H-7, H-8), 5.93 (1H, s, very fine coupling H-2); δ_C($CDCl_3$) 19.6 (Me), 25.3 (Me), 26.7 (Me), 33.8 (C-4), 49.6 (C-5), 67.0 (C-8), 70.5 (C-6), 76.8 (C-7), 109.4 (>C<), 130.2 (C-2), 180.1 (C-3), 211.0 (C-1); m/z (E.I.) no $(M)^+$, 211 $(M-Me)^+$, 208 $(M-H_2O)^+$, 125, 101, 96; (C.I.) 227 $(M+1)^+$ [Found: $(M-Me)^+$, 211.0939. $C_{11}H_{15}O_4$ requires $(M-Me)^+$, 211.0968].

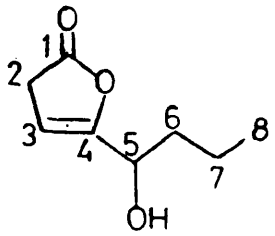
EXPERIMENTAL TO CHAPTER 3

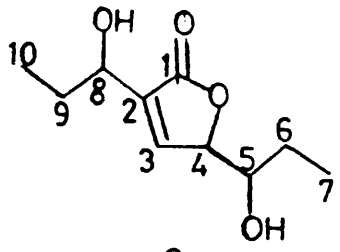
Aldol Chemistry of But-2-en-4-olide and its Silyl Dienolate [2-(Trialkylsiloxy)furan]

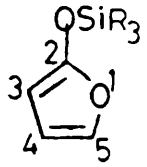
For convenience, when considering spectra, the compounds discussed in this section are numbered as exemplified below. However, elsewhere when numbering compounds, the IUPAC nomenclature and numbering has been used.

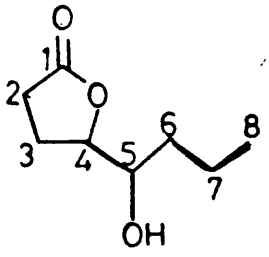












But-2-en-4-olide[76] (2).-Following the literature preparation and starting with furfural (48.0 g, 0.5 mmol), formic acid (46.5 g, 1.0 mmol), sodium sulfate (50 g), and potassium carbonate (17.5 g), the title compound (2) (20.6 g, 49%) was obtained as a pale-yellow liquid (b.p. 94 → 97 °C at 19 mmHg, lit.,[76] b.p. 95-96 °C at 19 mmHg). The spectral data of the product was in agreement with published data;[76] ν_{max} (film) 3080, 2920, 1730 (CO), 1610, 1590 (C=C) cm^{-1}; δ_H ($CDCl_3$) 4.90 (2H, dd, J = 2.0, 1.5 Hz, H-4), 6.18 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.56 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) 72.0 (C-4), 121.3 (C-2), 152.8 (C-3), 173.6 (C-1).

A number of reaction conditions were tried to prepare silyl dienolates of but-2-en-4-olide efficiently, the most successful methods are outlined below.

2-(Trimethylsiloxy)furan (88).(1) Triethylamine as base[77] (thermodynamic conditions). To a pre-cooled (0 °C) mixture of triethylamine (5.7 cm^3, 41.0 mmol) and freshly distilled trimethylsilyl chloride (5.2 cm^3, 41.0 mmol), was added dropwise with stirring, but-2-en-4-olide (2) (3.4 g, 40.0 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4.5 h, diluted with pentane (50 cm^3). Any insoluble triethylamine salts were filtered off and washed with pentane (30 cm^3). The pentane filtrate and washings were combined and evaporated *in vacuo* (no heat) to leave a viscous orange liquid. Distillation of this liquid gave 2-(trimethylsiloxy)furan (88) (3.2 g, 51%) as a colourless sweet-smelling liquid (b.p. 39-42 °C at 15 mmHg, lit.,[77] b.p. 42-50 °C at 17 mmHg). The spectra data of (88) were commensurate with published data;[77] ν_{max} (liquid film) 2960, 2890, 1595, 1510, 1350 cm^{-1}; δ_H ($CDCl_3$) 0.26 (9H, s, Me_3Si), 5.07 (1H, dd, J = 3.0, 1.0 Hz, H-3), 6.18 (1H, dd, J = 3.0, 2.5 Hz, H-4), 6.78 (1H, dd, J = 2.5, 1.0 Hz, H-5); δ_C ($CDCl_3$) 0.4 (C-Si), 83.1 (C-3), 110.9 (C-4), 132.2 (C-5), 156.5 (C-2); m/z (C.I.) 157 $(M+1)^+$, 73.

Compound (88) is air and moisture sensitive; when left to stand in air at room temperature for several days it reverts to the starting lactone (2) and unidentified silyl material. The silyl dienolate (88) was used immediately, or stored at -20 °C under a nitrogen atmosphere.

(2) LDA as base (kinetic conditions)

Treatment of but-2-en-4-olide (2) at -78 °C with LDA (1.1 eq) for 40 min gave a carbanion which was quenched with trimethylsilyl chloride (1.1 eq) at -78 °C. The mixture was allowed to warm to ambient temperature, then diluted with pentane and washed with water. The organic layers were collected, dried ($MgSO_4$) and concentrated *in vacuo* (no heat) to leave a brown liquid. Distillation of the crude product afforded (88) in *ca.* 40% yield.

(3) Sodium hydride as base

But-2-en-4-olide (2) was treated with NaH (1.1 eq) in DMF at 0 °C for *ca.* 30 min. The anion which formed was quenched with trimethylsilyl chloride. A multi component mixture resulted. The experiment was discontinued.

Since we started our research on aldol chemistry of (2) and (88), both compounds have become commercially available.

2-(t-Butyldimethylsiloxy)furan (93).-(1) LDA as base (kinetic conditions). To a solution of di-isopropylamine (2.37 cm^3, 17.0 mmol) in freshly distilled THF (10 cm^3) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium (17.0 mmol). After stirring for 5 min, the solution was cooled to -78 °C and but-2-en-4-olide (2) (1.28 g, 15.0 mmol) in 5:1 THF:DMPU (6 cm^3) was added dropwise. The mixture was stirred at -78 °C for 40 min, quenched with *t*-butyldimethylsilyl chloride (2.3 g, 15.0 mmol) in THF (10 cm^3) and then allowed to warm to ambient temperature. The mixture was diluted with pentane (150 cm^3) and washed with water (2 x 20 cm^3). The organic layers were combined, dried (Na_2SO_4) and the solvent removed *in vacuo* (no heat) to leave a brown oil. Purification of the oil by column chromatography [neutral alumina, petrol-EtOAc (9:1)] gave the *title compound* (93) (1.50 g, 50%) as a pale-yellow oil; ν_{max} (liquid film) 3100, 2920, 2850, 1600, 1510, 1460 cm^{-1}; δ_H ($CDCl_3$) 0.14 (6H, s, Me_2Si), 0.87 (9H, s, *t*-Bu), 5.01 (1H, dd, J = 3.0, 1.0 Hz, H-3), 6.11 (1H, dd, J = 3.0, 2.5 Hz, H-4), 6.71 (1H, dd, J = 2.5, 1.0 Hz, H-5); δ_C ($CDCl_3$) 25.4 (*t*-Bu), 83.0 (C-3), 110.5 (C-4), 132.2 (C-5), 156.9 (C-2); m/z (E.I.) 198 $(M)^+$, 73.

(2) Triethylamine as base (thermodynamic conditions)

Following the experimental procedure used in the triethylamine-mediated preparation of (88), compound (93) (25%) was obtained, together with starting lactone (2).

General procedure for the stannic chloride-mediated aldol reaction between 2-(trimethylsiloxy)furan (88) and prochiral aldehydes

To a solution of 2-(trimethylsiloxy)furan (88) (15 mmol) in freshly distilled DCM (10 cm^3) was added the aldehyde (18.0 mmol) and stannic chloride (*ca.* 4 drops, 0.1 eq). The reaction mixture was stirred for typically 60 min, quenched with either saturated sodium metabisulphate solution or water and extracted with EtOAc (3 x 25 cm^3). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude aldol product. The crude product was purified by silica gel column chromatography. The yields of the aldol products were determined by g.l.c, analysis (internal standard and correcting for recovered starting materials) and/or by isolation of the aldol adducts. Diastereoisomer ratios were determined by g.l.c. analysis, unless otherwise stated.

The following aldols have been prepared by the above general procedure.

4-(1'-Hydroxyundecyl)but-2-en-4-olide (94).-Starting with 2-(trimethylsiloxy)furan (88) (2.36 g, 15.0 mmol) and undecanal (3.00 g, 18.0 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 60 min), the *title compound* (94) (3.01 g, 80%) was obtained as a white crystalline solid (m.p. 91-92 °C). After correcting for the recovery of but-2-en-4-olide (2), the g.l.c. yield of (94) was 86%. The ratio of *syn*:*anti* diastereoisomers was 98:2. Only the *syn* diastereoisomer was characterised; ν_{max} ($CHCl_3$) 3360 (OH), 3100, 1715 (CO), 1600 (C=C), 1375 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, t, J = 7.0 Hz, H-15), 1.20-1.36 (16H, virtual coupling, H-7 → H-14), 1.58 (2H, m, H-6), 2.92 (1H, d, J = 5.5 Hz, OH), 3.78 (1H, m, H-5), 5.02 (1H, dt, J = 4.5, 2.0 Hz, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.50 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) 14.1 (C-15), 22.7 (C-14), 25.6 (C-13), 29.3, 29.4, 29.5, 29.6 (C-8 → C-12), 31.9 (C-7), 33.2 (C-6), 71.6 (C-5), 86.4 (C-4), 122.5 (C-2), 154.3 (C-3), 173.4 (C-1); m/z (C.I.) 255 $(M+1)^+$, 237 $(M+1-H_2O)^+$, 171, 84 $(C_4H_4O_2)^+$;

[Found: C, 70.9; H, 10.2. $C_{16}H_{26}O_3$ requires C, 70.9; H, 10.2%].

4-(1'-Hydroxyhexyl)but-2-en-4-olide (95).-Starting with 2-(trimethylsiloxy)furan (88) (3.10 g, 20.0 mmol) and hexanal (2.40 cm^3, 24.0 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 150 min), the *title compound* (95) (2.83 g, 77%) was obtained as a yellow oil. A sample of the crude product was purified by column chromatography [silica gel, petrol-EtOAc (3:2)] and gave the *anti* isomer as a white crystalline solid (recrystallised ether, m.p. 61 °C). The ratio of *syn*:*anti* diastereoisomers as determined by g.l.c. of the crude product was 94:6; ν_{max} ($CHCl_3$) diastereomeric mixture 3360 (OH), 3090, 1770 (C=O), 1595 (C=C), 820 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 0.88 (3H, t, J = 7.0 Hz, H-10), 1.35 (6H, bs, virtual coupling, H-7, H-8, H-9), 1.65 (2H, m, H-6), 3.83 (1H, m, H-5), 4.45 (1H, bs, OH), 4.98 (1H, dt, J = 5.0, 1.5 Hz, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.65 (1H, dd, J = 6.0, 1.5 Hz, H-3); *syn* isomer 0.88 (3H, t, J = 7.0 Hz, H-10), 1.35 (6H, bs, H-7, H-8, H-9), 1.65 (2H, bs, H-6), 3.83 (1H, m, J = 4.5 Hz, H-5), 4.45 (1H, bs, OH), 5.06 (1H, dt, J = 4.0, 2.0 Hz, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.58 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 13.6 (C-10), 22.2 (C-9), 24.9 (C-8), 31.2 (C-7), 32.7 (C-6), 71.0 (C-5), 86.3 (C-4), 122.0 (C-2), 154.4 (C-3), 173.5 (C-1), *syn* isomer as above, except 32.6 (C-6), 70.8 (C-5), 86.2 (C-4), 121.9 (C-2), 154.6 (C-3), 173.5 (C-1); m/z (C.I.) diastereomeric mixture 185 $(M+1)^+$, 167 $(M+1-H_2O)^+$, 84 $(C_4H_4O_2)^+$; [Found: C, 65.0; H, 8.7. $C_{11}H_{16}O_3$ requires C, 65.2; H, 8.8%].

An analogous reaction was performed with the *t*-butyldimethylsilyl dienolate of but-2-en-4-olide (93) (1.6 mmol), hexanal (1.6 mmol) and $SnCl_4$ (2 drops) under identical conditions to those described above. The aldol product (95) was obtained in 86% yield. The ratio of *syn*:*anti* diastereosimers was *ca.* 90:10. Spectral data of the product (95) was identical with data reported earlier.

4-(1'-Hydroxyethyl)but-2-en-4-olide (99).-Starting with 2-(trimethylsiloxy)furan (88) (0.32 g, 2.0 mmol) and ethanal (0.10 g, 2.4 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 60 min), the *title compound* (99) (0.17 g, 67%) was obtained as a yellow oil. After correcting for the recovery of but-2-en-4-olide, the overall g.l.c. yield was >95%. The ratio of *syn*:*anti* diastereoisomers as determined by g.l.c. analysis was 87:13; ν_{max} (film) diastereomeric mixture 3410 (OH), 1740 (C=O) cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.32 (3H, d, J = 6.5 Hz, H-6), 2.97 (1H,

s, OH), 4.06 (1H, qd, J = 6.5, 5.0 Hz, H-5), 4.96 (1H, ddd, J = 5.0, 2.0, 1.5 Hz, H-4), 6.20 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.59 (1H, dd, J = 6.0, 1.5 Hz, H-3), *syn* isomer 1.33 (3H, d, J = 6.5 Hz, H-6), 2.43 1H, s, OH), 3.94 (1H, qd, J = 6.5, 5.5 Hz, H-5), 4.94 (1H, ddd, J = 5.5, 2.0, 1.5 Hz, H-4), 6.20 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.46 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 18.8 (C-6), 67.5 (C-5), 86.9 (C-4), 122.7 (C-2), 153.6 (C-3), 173.2 (C-1), *syn* isomer 18.8 (C-6), 68.3 (C-5), 87.1 (C-4), 122.9 (C-2), 153.4 (C-3), 173.5 (C-1); m.z (C.I.) diastereomeric mixture 129 $(M+1)^+$, 111 $(M+1-H_2O)^+$, 85; [Found: C, 56.3; H, 6.3 $C_6H_8O_3$ requires C, 56.3; H, 6.3%].

4-(1'-Hydroxypropyl)but-2-en-4-olide (100).-Starting with 2-(trimethylsiloxy)furan (88) (0.32 g, 2.0 mmol) and propanal (0.13 g, 2.4 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 60 min), the *title compound* (100) (0.15 g, 52%) was obtained as a yellow oil, along with but-2-en-4-olide (2). The overall g.l.c. yield was 70%, after correcting for the recovery of (2). The ratio of *syn*:*anti* diastereoisomers was 81:19 as determined by g.l.c. analysis; ν_{max} (liquid film) diastereomeric mixture 3440 (OH), 1785 (CO), 1600 (C=C) cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.04 (3H, t, J = 6.5 Hz, H-7), 1.60 (2H, m, H-6), 3.54 (1H, bs, OH), 3.75 (1H, m, H-5), 4.99 (1H, m, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.64 (1H, dd, J = 6.0, 1.5 Hz, H-3), *syn* isomer 1.02 (3H, t, J = 6.5, H-7), 1.60 (2H, m, H-6), 3.54 (1H, bs, OH), 3.74 (1H, dt, H-5), 5.06 (1H, dt, J = 2.0 Hz, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.56 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 9.7 (C-7), 26.0 (C-6), 72.4 (C-5), 86.0 (C-4), 122.0 (C-2), 154.4 (C-3), 173.4 (C-1); *syn* isomer 9.8 (C-7), 25.8 (C-6), 72.3 (C-5), 85.9 (C-4), 121.9 (C-2), 154.6 (C-3), 173.5 (C-1); m/z (C.I.) diastereomeric mixture 143 $(M+1)^+$, 125 $(M+1-H_2O)^+$, 85, [Found: C, 58.9; H, 6.9. $C_7H_{10}O_3$ requires C, 59.2; H, 7.0%].

4-(1'-Hydroxy-2'-methylpropyl)but-2-en-4-olide (101).-Starting with 2-(trimethylsiloxy)furan (88) (0.32 g, 2.0 mmol) and 2-methylpropanal (0.18 g, 2.5 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 60 min), the *title compound* (101) (0.25 g, 80%) was obtained as a yellow oil along with but-2-en-4-olide (2) (0.02 g). After correcting for the recovery of (2), the g.l.c. yield of (101) was 91%. The ratio of *syn*:*anti* diastereoisomers was 94:6; ν_{max} (film) diastereomeric mixture 3430 (OH), 3100, 1740 (CO), 1385, 1360 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.02 (3H, d,

J = 7.0 Hz, Me), 1.04 (3H, d, J = 7.0 Hz, Me), 1.88 (1H, m, J = 7.0 Hz, H-6), 3.44 (1H, bs, OH), 3.55 (1H, dd, J = 7.0, 5.5 Hz, H-5), 5.09 (1H, dt, J = 5.5, 2.0 Hz, H-4), 6.16 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.65 (1H, dd, J = 6.0, 1.5 Hz, H-3), *syn* isomer 1.05 (3H, d, J = 7.0 Hz, Me), 1.07 (3H, d, J = 7.0 Hz, Me), 1.94 (1H, m, J = 7.0 Hz, H-6), 2.45 (1H, bs, OH), 3.45 (1H, dd, J = 7.0 Hz, 4.0 Hz, H-5), 5.17 (1H, dt, J = 4.0, 2.0 Hz, H-4), 6.18 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.47 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 17.3 (Me), 18.8 (Me), 30.9 (C-6), 75.9 (C-5), 84.4 (C-4), 122.2 (C-2), 154.8 (C-3), 173.5 (C-1); *syn* isomer 17.8 (Me), 19.4 (Me), 31.6 (C-6), 76.4 (C-5), 84.6 (C-4), 122.4 (C-2), 154.4 (C-3), 173.4 (C-1); m/z (C.I.) diastereomeric mixture 157 $(M+1)^+$, 139 $(M+1-H_2O)^+$ 85 $(C_4H_4O_2)^+$; [Found: C, 61.3; H, 8.0. $C_8H_{12}O_3$ requires C, 61.5; H, 7.7%].

4-(2',2'-Dimethyl-1'-hydroxypropyl)but-2-en-4-olide (102).-Starting with 2-(trimethylsiloxy)furan (88) (0.60 g, 5.0 mmol) and 2,2-dimethyl propanal (0.60 cm^3, 5.5 mmol) and following the general procedure for stannic chloride-mediated aldol reactions of (88) (reaction time 160 min), the *title compound* (102) (0.46 g, 54%) along with but-2-en-4-olide (2) (0.07 g) was obtained as a pale-yellow oil. Separation of the diastereoisomers by column chromatography [silica gel, petrol-EtOAc (2:1)] gave the *syn* isomer (72%) and *anti* isomer (28%). Yield corrected for the recovery of (2) was 69%. G.l.c. analysis of the crude mixture showed a *syn*:*anti* diastereoisomer ratio of 70:30; ν_{max} ($CHCl_3$) diastereomeric mixture 3590 (OH), 2950, 2860, 1740 (CO), 1595 (C=C), 815 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 1.06 (9H, s, *t*-Bu), 2.40 (1H, bs, OH), 3.54 (1H, d, J = 5.0 Hz, H-5), 5.14 (1H, dt, J = 5.0, 2.0 Hz, H-4), 6.17 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.64 (1H, dd, J = 6.0, 1.5 Hz, H-3), *syn* isomer 1.07 (9H, s, *t*-Bu), 2.25 (1H, bs, OH), 3.46 (1H, d, J = 2.0 Hz, H-5), 5.26 (1H, q, J = 2.0 Hz, H-4), 6.15 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.48 (1H, dd, J = 6.0, 1.5 Hz, H-3); δ_C ($CDCl_3$) *anti* isomer 26.3 (Me_3), 34.5 (C-6), 79.3 (C-5), 84.2 (C-4), 122.3 (C-2), 155.5 (C-3), 173.5 (C-1), *syn* isomer 26.4 (Me_3), 35.3 (C-6), 77.7 (C-5), 82.4 (C-4), 121.8 (C-2), 156.0 (C-3), 173.4 (C-1); m/z (C.I.) diastereomeric mixture 171 $(M+1)^+$, 153 $(M+1-H_2O)^+$, 87, 85; [Found: C, 70.6; H, 9.1. $C_{10}H_{16}O_2$ requires C, 71.4; H, 9.6%].

4-(1'-Hydroxy-1'-phenylmethyl)but-2-en-4-olide (103).-Starting with 2-(trimethylsiloxy)furan (88) (0.32 g, 2.0 mmol) and freshly distilled benzaldehyde (0.24 g, 2.4 mmol) and following the general procedure for $SnCl_4$-mediated aldol reactions of (88) (reaction time 60 min), the *title compound* (103) (0.23 g, 60%) was obtained as a pale-yellow oil, along with but-2-en-4-olide (2) (0.02 g). After correction for the recovery of (2), the g.l.c. yield was 80%. G.l.c. analysis of the mixture gave a *syn:anti* diastereoisomer ratio of 88:12; ν_{max} (film) diastereomeric mixture 3430 (OH), 3070, 1750 (CO), 1600 cm^{-1}; δ_H ($CDCl_3$) *anti* isomer 3.30 (1H, bs, OH), 5.05 (1H, d, J = 4.0 Hz, H-5), 5.15 (1H, m, H-4), 6.13 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.16 (1H, dd, J = 6.0, 1.5 Hz, H-3), 7.32-7.40 (5H, m, H-aromatic), *syn* isomer 3.30 (1H, bs, OH), 4.69 (1H, d, J = 7.0 Hz, H-5), 5.15 (1H, m, H-4), 6.07 (1H, dd, J = 6.0, 2.0 Hz, H-2), 7.32 (1H, dd, J = 6.0, 1.5 Hz, H-3), 7.32-7.40 (5H, m, H-aromatic); δ_C ($CDCl_3$) *anti* isomer 72.9 (C-5), 86.9 (C-4), 123.1 (C-2), 126.0, 126.7, 128.7, 137.7 (C-aromatic), 153.0 (C-3), 173.5 (C-1); *syn* isomer 75.3 (C-5), 86.6 (C-4), 122.9 (C-2), 126.0, 126.7, 128.7, 137.8 (C-aromatic), 153.3 (C-3), 173.5 (C-1); m/z (C.I.) diastereomeric mixture 191 $(M+1)^+$, 173 $(M+1-H_2O)^+$ 107, 85; [Found: C, 69.7; H, 5.2. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%].

General procedure for the aldol reaction between 2-(trimethylsiloxy)-furan (88) and ethanal mediated by different Lewis acids

To a solution of 2-(trimethylsiloxy)furan (0.32 g, 2.0 mmol) and ethanal (0.11 g, 2.4 mmol) in freshly distilled DCM (5 cm^3) at -78 °C under an inert gas atmosphere, was added *ca.* 0.1 → 0.3 equivalents of the Lewis acid (LA). The reaction mixture was stirred at -78 °C for 60-90 min, then quenched with saturated ammonium chloride solution and worked up in the usual way [see preparation of (99) from (88) mediated by $SnCl_4$] to afford (99) as a yellow oil. The yields and diastereoisomer ratios of the crude aldol product were determined by g.l.c. analysis using an internal standard and correcting for recovered (2). The results of the above study on diastereoselectivity of aldol reactions of (88) with ethanal mediated by different Lewis acids are cited in Scheme 86 and Table 32 in Section 3.3.3. All the reactions were done on a 2 mmol scale in dry DCM at -78 °C, reaction time 60-90 min.

Aldol reaction of 2-(trimethylsiloxy)furan (88) and ethanal mediated by tetra-n-butylammonium fluoride (TBAF).-To a solution of 2-(trimethylsiloxy)furan (88) (0.32 g, 2.0 mmol) and ethanal (0.11 g, 2.4 mmol) in DCM (5 cm^3) at -78 °C under a nitrogen atmosphere was added TBAF (0.1 cm^3 of a 1M solution in THF, 0.05 eq). The reaction mixture was stirred at -78 °C for 60 min, then quenched with 2N hydrochloric acid (1 cm^3) and allowed to warm to ambient temperature. The solvent was removed under reduced pressure to leave an oily suspension which was washed with EtOAc (4 x 10 cm^3). The EtOAc washings were combined, dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil. G.l.c. analysis of the oil showed that it consisted of a mixture of 4-(1'-hydroxyethyl)but-2-en-4-olide (99) and but-2-en-4-olide (2). The aldol (99) was separated from (2) by column chromatography [silica gel, petrol-EtOAc (1:1)]. After correcting for the recovery of (2), the overall yield of (99) was 71%. The ratio of *syn:anti* diastereoisomers as determined by g.l.c. was 42:58. The spectral data of the product were commensurate with data reported earlier for aldol (99).

Determination of the relative stereochemistry of 4-substituted but-2-en-4-olide aldols

In order to determine the relative stereochemistry of the 4-substituted but-2-en-4-olide aldols. The major diastereoisomers of aldol adducts (94) and (95) [produced by $SnCl_4$-mediated reactions of (88)] were catalytically reduced to the 2-substituted butan-4-olides (96) and (97) respectively. The spectra data of aldols (96) and (97) were then compared with spectral data of compounds of known stereochemistry (see Section 3.3.1).

4-(1'-Hydroxyundecyl)butan-4-olide (96).-To a solution of aldol (94) (0.45 g, 1.8 mmol) (single diastereoisomer) in EtOAc (30 cm^3) was added 10% palladium on carbon catalyst (50 mg). The resultant suspension was stirred at RT for 3 h under one atmosphere of hydrogen. The catalyst was then removed by filtration through celite and the filtrate evaporated *in vacuo* to afford the title compound (96) (0.45 g, 99%) as a white solid, m.p. 64 °C; ν_{max} ($CHCl_3$) 3400 (OH), 1740 (CO) cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, t, J = 7.0 Hz, H-15), 1.26 (16H, virtual coupling H-7 → H-14), 1.53 (2H, m, H-6), 2.20 (2H, bm, J_{gem} = 13.0 Hz, H-3), 2.54 (1H, bs, OH), 2.57 (2H, m, J_{gem} = 18.0 Hz, H-2), 3.57 (1H, m, J = 6.5, 4.5 Hz, H-5),

4.43 (1H, dt, J = 7.0, 4.5 Hz, H-4); δ_C ($CDCl_3$) 14.0 (C-15), 22.7 (C-14), 23.9 (C-3), 25.5 (C-13), 28.7 (C-2), 29.3, 29.5, 29.6 (C-8 → C-12), 31.9 (C-7), 33.0 (C-6), 73.5 (C-5), 83.1 (C-4), 177.6 (C-1); m/z (C.I.) 257 $(M+1)^+$, 239 $(M+1-H_2O)^+$.

A comparison of the spectral data of aldol (96) with literature data for the *syn* diastereoisomer of 4-(1'-hydroxyundecyl)butan-4-olide[78] indicated that compound (96) is a *syn* diastereoisomer.

4-(1'-Hydroxyhexyl)butan-4-olide (97).-To a solution of 4-(1'-hydroxyhexyl)but-2-en-4-olide (95) (0.21 g, 1.1 mmol) (single racemic diastereoisomer) in EtOAc (20 cm^3) was added 10% palladium on carbon catalyst (26 mg). The resultant suspension was hydrogenated (1 atmosphere of H_2, RT for 18 h) to give, after the usual work-up, the title compound (97) (0.20 g, 95%) as a clear crystalline solid which melted at hand temperature; ν_{max} ($CHCl_3$) 3400 (OH), 1760 (CO) cm^{-1}; δ_H ($CDCl_3$) 0.89 (3H, t, J = 6.5 Hz, H-10), 1.31 (5H, m, H-7a, H-8, H-9), 1.58 (3H, m, H-6, H-7b), 2.14 (1H, m, J_{gem} 13.0 Hz, H-3a), 2.25 (1H, m, J_{gem} = 18.0 Hz, H-3b), 2.54 (1H, m, J = 18.0 Hz, H-2a), 2.62 (1H, m, J = 18.0 Hz, H-2b), 2.82 (1H, d, J = 6.5 Hz, OH), 3.57 (1H, m, H-5) 4.42 (1H, dt, J = 7,5, 4.5 Hz, H-4); δ_C ($CDCl_3$) 13.8 (C-10), 22.4 (C-9), 23.9 (C-3), 25.0 (C-8), 28.6 (C-2), 31.5 (C-7), 32.7 (C-6), 73.2 (C-5), 83.0 (C-4), 177.6 (C-1); m/z (C.I.) 187 $(M+1)^+$, 169 $(M+1-H_2O)^+$; [Found: C, 64.7; H, 9.7. Calc. for $C_{10}H_8O_3$: C, 64.5; H, 9.7%].

A comparison of the ^1H n.m.r. spectral data of the product (97) with literature data[79] for the *syn* diastereoisomer of 4-(1'-hydroxyhexyl)butan-4-olide confirmed product (97) as the *syn* diastereoisomer.

Reactions between 2-(trimethylsiloxy)furan (88) and aldehydes mediated by Eu(fod)$_3$

The following compounds have been prepared by reactions between silyl dienolate (88) and aldehydes in the presence of catalytic amounts of the lanthanide reagent Eu(fod)$_3$.

2-(1'-Hydroxyethyl)but-2-en-4-olide (109).-To a solution of 2-(trimethylsiloxy)furan (88) (1.25 g, 8.0 mmol) in freshly distilled THF (15 cm^3) was added ethanal (1.57 g, 10.0 mmol) and (0.3 cm^3) of a chloroform solution of $Eu(fod)_3$ (46 mg/cm^3). The reaction mixture was stirred at room temperature for 168 h under an argon atmosphere. Evaporation of the solvent under reduced pressure left an oily residue which was treated with dilute hydrochloric acid (1 cm^3 of 2N solution in 30 cm^3 of water) and the aqueous phase washed with DCM (2 x 25 cm^3), neutralised with saturated aqueous sodium hydrogen cabronate solution (3 cm^3). After evaporation of the solvent under reduced pressure, the residue was extracted with EtOAc (25 cm^3). The organic phase was collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave a brown oil. Purification by column chromatography [silica gel, DCM-EtOAc (20:1 → 4:1)] gave a yellow oil which was identified by n.m.r. spectroscopy as *2-(1'-hydroxyethyl)but-2-en-4-olide* (109). A sample of the crude product was analysed by g.l.c. using an internal standard. After correction for the recovery of but-2-en-4-olide (2), the yield of the *title compound* (109) was 68%; ν_{max} (film) 3440 (OH), 3100, 1730 (CO), 1375 cm^{-1}; δ_H ($CDCl_3$) 1.41 (3H, d, J = 6.0 Hz, H-6), 3.31 (1H, bs, OH), 4.53 (1H, bs, H-5), 4.88 (2H, t, J = 1.5 Hz, H-4), 7.37 (1H, q, J = 1.5 Hz, H-3); δ_C ($CDCl_3$) 21.9 (C-6), 63.2 (C-5), 70.8 (C-4), 136.0 (C-2), 145.2 (C-3), 173.2 (C-1); m/z (E.I.) 128 $(M)^+$, 111 $(M-H_2O)^+$, 84; [Found: C, 56.1; H, 6.3. $C_6H_8O_3$ requires: C, 56.3; H, 6.3%].

A $Pr(fod)_3$-catalysed reaction of 2-(trimethylsiloxy)furan (88) and ethanal under identical conditions to those described for $Eu(fod)_3$-catalysed reactions gave compounds (109) (56%) and (99) (24%). The spectroscopic data on the products were identical to data previously quoted for compounds (109) and (99).

2-(1'-Hydroxypropyl)but-2-en-4-olide (110).-To a solution of 2-(trimethylsiloxy)furan (88) (2.50 g, 16.0 mmol) in freshly distilled THF (25 cm^3) was added propanal (1.40 g, 24.0 mmol) and (0.5 cm^3) of a chloroform solution of $Eu(fod)_3$ (46 mg/cm^3). The reaction mixture was stirred at 40 °C under an argon atmosphere for 72 h. Evaporation under reduced pressure left an oily residue which was treated with dilute hydrochloric acid, extracted with EtOAc (3 x 20 cm^3) and neutralised with saturated sodium hydrogen carbonate solution. The

organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil. Column chromatography [silica gel, petrol-EtOAc (1 : 2)] on the oil gave the *title compound* (110), together with a *dehydration product* (113), but-2-en-4-olide (2) and some uncharacterised by-products. A sample of the crude product was analysed by g.l.c. using an internal standard. After correcting for recovered (2), the yields of (110) and (113) were 54% and 21% respectively.

2-(1'-Hydroxypropyl)but-2-en-4-olide (110): ν_{max} 3450 (OH), 3095, 1725 (CO), 1375 cm^{-1}; δ_H ($CDCl_3$) 1.00 (3H, t, J = 7.0 Hz, H-7), 1.84 (2H, m, J = 7.0 Hz, H-6), 3.20 (1H, bs, OH), 4.46 (1H, bm, H-5), 4.86 (2H, t, J = 1.5 Hz, H-4), 7.38 (1H, q, J = 1.5 Hz, H-3); δ_C ($CDCl_3$) 9.4 (C-7), 28.3 (C-6), 68.0 (C-5), 70.4 (C-4), 136.2 (C-2), 145.3 (C-3), 173.2 (C-1); m/z (C.I.) 143 $(M+1)^+$, 125 $(M+1-H_2O)^+$; [Found: C, 58.2; H, 7.0. $C_7H_{10}O_3$ requires: C, 59.2; H, 7.1%].

(E)-2-(Prop-1'-enyl)but-2-en-4-olide (113): ν_{max} (film) 3120, 1780, 1750 (CO), 1370 cm^{-1}; m/z (E.I.) 124 $(M)^+$, 95 $(M-Et)^+$; δ_H ($CDCl_3$) 1.85 (3H, dm, J = 7.0, 1.0 Hz, Me), 4.80 (2H, dd, J = 1.5, 1.0 Hz, H-4), 6.15 (1H, dq, J = 16.0, 1.0 Hz, H-5), 6.82 (1H, dqd, J = 16.0, 7.0, 1.5 Hz, H-6), 7.13 (1H, m, J = 1.5, 1.0 Hz, H-3).

2-(1'-Hydroxy-2'-methylpropyl)but-2-en-4-olide (111).-To a solution fo 2-(trimethylsiloxy)furan (88) (2.50 g, 16.0 mmol) in freshly distilled THF (25 cm^3) was added 2-methylpropanal (1.80 g, 25.0 mmol) and (0.5 cm^3) of a chloroform solution of $Eu(fod)_3$ (46 mg/cm^3). The reaction mixture was sitrred at 60 °C for 48 h under an argon atmosphere. Evaporation of the solvent under reduced pressure left an oily residue which was treated with dilute hydrochloric acid (1.5 cm^3 of 2N solution in 40 cm^3 of water) and extracted with EtOAc (3 x 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil. Column chromatography on silica gel gave the *title compound* (111), but-2-en-4-olide (2) and small amounts of uncharacterised by-products. G.l.c. analysis of a sample of the crude product using an internal standard and correcting for recovery of (2) gave *2-(1'-hydroxy-2'-methylpropyl)but-2-en-4-olide* (111) in 65% yield; ν_{max} (film) 3450 (OH), 3100, 1730 (CO), 1380, 1365 cm^{-1}; δ_H ($CDCl_3$) 0.88 (3H, d, J = 7.0 Hz, Me), 0.98 (3H, d, J = 7.0 Hz, Me), 2.08 (1H, m, J = 4.5 Hz, H-6), 3.00 (1H, bs, OH), 4.30 (1H, m, J = 4.5, 1.5 Hz, H-5), 4.86 (2H, t,

J = 1.5 Hz, H-4), 7.37 (1H, q, J = 1.5 Hz, H-3); δ_C ($CDCl_3$) 16.5 (Me), 18.9 (Me), 32.1 (C-6), 70.5 (C-4), 72.0 (C-5), 135.3 (C-2), 146.2 (C-3), 173.3 (C-1); m/z (C.I.) 157 $(M+1)^+$, 139 $(M+1-H_2O)^+$; [Found: C, 61.3; H, 7.9. $C_8H_{12}O_3$ requires; C, 61.5; H, 7.7%].

2-(1'-Hydroxy-1'-phenylmethyl)but-2-en-4-olide (112).-To a stirred solution of 2-(trimethylsiloxy)furan (2.50 g, 16.0 mmol) in freshly distilled THF (85 cm^3) was added benzaldehyde (2.12 g, 20.0 mmol) and (0.5 cm^3) of a chloroform solution of $Eu(fod)_3$ (46 mg/cm^3). The reaction mixture was stirred at 60 °C for 48 h under an argon atmosphere. Evaporation under reduced pressure gave an oily residue which was treated with dilute hydrochloric acid (1.5 cm^3 of 2N solution in 40 cm of water) and extracted with EtOAc (3 x 20 cm^3). The organic layers were combined, dried ($MgSO_4$) and evaporated *in vacuo* to leave a yellow oil which contained the *title compound* (112), but-2-en-4-olide (2) and some uncharacterised by-products. G.l.c. analysis of the crude product, using an internal standard and correcting for recovery of (2) gave *2-(1'-hydroxy-1'-phenylmethyl)but-2-en-4-olide* (112) in 73% yield; ν_{max} (film) 3430 (OH), 3070, 1740 (CO) cm^{-1}; δ_H ($CDCl_3$) 3.80 (1H, bs, OH), 4.72 (2H, t, J = 1.5 Hz, H-4), 5.50 (1H, m, J = 1.5 Hz, H-5), 7.18 (1H, q, J = 1.5 Hz, H-3), 7.23-7.42 (5H, m, H-aromatics); δ_C ($CDCl_3$) 69.0 (C-5), 70.7 (C-4), 136.3 (C-2), 126.5, 128.5, 128.6, 140.3 (C-aromatics), 146.4 (C-3), 173.1 (C-1); m/z (E.I.) 190 $(M)^+$, 172 $(M-H_2O)^+$, 144, 108; [Found: C, 69.2; H, 5.5. $C_{11}H_{10}O_3$ requires: C, 69.5; H, 5.3%].

Reaction between the lithium dienolate of but-2-en-4-olide (2) and hexanal [example of general procedure of LDA-mediated aldol reaction of (2)].-To a solution of di-isopropylamine (1.45 cm^3, 11.0 mmol) in distilled THF (20 cm^3) at 0 °C under a nitrogen atmosphere was added *n*-butyllithium (11.0 mmol). After 10 min, the solution was cooled to -78 °C and but-2-en-4-olide (2) (0.72 cm^3, 10.0 mmol) in dry THF (5 cm^3) was added dropwise. After stirring for 10 min, hexanal (1.25 cm^3, 10.5 mmol) in THF (5 cm^3) was added and the mixture was stirred at -78 °C for 65 min, then quenched with saturated aqueous ammonium chloride solution (5 cm^3) and allowed to warm to ambient temperature. The solvent was removed by evaporation to give a cloudy yellow suspension,

which was partitioned between EtOAc (150 cm^3) and water (50 cm^3). The organic layer was separated, washed with water (2 x 40 cm^3), collected, dried ($MgSO_4$) and evaporated *in vacuo* to leave an orange oil (1.70 cm^3). T.l.c. analysis of the oil [petrol-EtOAc (1:1)] indicated that it consisted of mainly two components, A and B, of almost identical R_f. Attempts to separate the components by flash column chromatography [silica gel, petrol-EtOAc (1:3 → 3:1)] gave typically fast-running fractions which contained predominantly component A, intermediate fractions consisting of a mixutre of components A and B, and slower moving fractions containing mostly component B. No fraction contained a single pure component. The fractions were concentrated and analysed by n.m.r. and m.s. Component A [yellow solid (impure)] was cautiously assigned as *2,4-di(1'-hydroxyhexyl)-but-2-en-4-olide* (118) (66% of crude mixture by ^1H n.m.r. analysis; mixture of stereoisomers). Component B (colourless oil) was assigned as *4-(1'-hydroxhhexyl)but-2-en-4-olide* (95) (34% of crude mixture by ^1H n.m.r. analysis, 12:88 mixture of *syn:anti* isomer).

Data on the products:

Compound (118): *ca.*∿60:40 mixture of two stereoisomers by ^1H n.m.r. analysis; ν_{max} ($CHCl_3$) mixture 3580, 3380 (OH), 2900, 1730 (CO), 1190, 1050 cm^{-1}; δ_H ($CDCl_3$) major isomer 0.88 (6H, bt, H-10, H-16), 1.20-1.80 [16H, bm, H-6 → H-9, H-12 → H-15), 3.95 [3H, m, H-5, 2(OH)], 4.46 (1H, t, J = 5.5 Hz, H-11), 4.86 (1H, d, J = 4.0 Hz, H-4), 7.33 (1H, s, H-3), minor isomer as above, except 3.78 (1H, m, H-5), 3.92 [2H, bs, 2(OH)], 4.46 (1H, t, J = 5.5 Hz, H-11), 4.92 (1H, m, H-4), 7.25 (1H, s, H-3); δ_C ($CDCl_3$) major isomer 13.9 (C-10, C-16), 22.4 (C-9, C-15), 24.8 (C-8, C-14), 3.15 (C-7, C-13), 33.0 (C-6), 35.5 (C-12), 66.4 (C-11), 71.2 (C-5), 84.3 (C-4), 139.2 (C-2), 145.6 (C-3), 172.6 (C-1), minor isomer as above, except 33.3 (C-6), 84.0 (C-4), 138.5 (C-2), 146.6 (C-3), 172.6 (C-1); m/z (C.I.) mixture 285 $(M+1)^+$, 267 $(M+1-H_2O)^+$, 249 $[M+1-2(H_2O)]^+$.

Compound (95): colourless oil, spectral data identical to data reported earlier for compound (95).

Reaction between the lithium dienolate of but-2-en-4-olide (2) and 2,2-dimethylpropanal.-Starting with but-2-en-4-olide (2) (0.36 cm^3, 5.0 mmol), 2,2-dimethylpropanal (0.61 cm^3, 5.5 mmol) and following the general experimental procedure for LDA-mediated reactions of (2) (reaction time 40 min), an orange oil (0.77 g) was obtained after work-up as before. T.l.c. analysis of the oil [petrol-EtOAc (1:2)] showed that it consisted of three components of very similar R_f. Medium pressure column chromatography on the crude mexture [silica gel, petrol-EtOAc (2:1 → 1:4)] gave column fractions containing mixtures of the three components. Only the major component could be obtained in a pure state. ^1H n.m.r. and ^{13}C n.m.r. analysis of the column fractions indicated that the crude mixture consisted of *4-(1'-hydroxy-2,2'-dimethylpropyl)but-2-en-4-olide* (102), *4-(1'-hydroxy-2,2'-dimethylpropyl)but-3-en-4-olide* (116) and *2,4-di(1'-hydroxy-2,2'-dimethylpropyl)but-2-en-4-olide* (120) in 80:16:4 ratio.

Data for the products:

Compound (102): yellow oil, mixture of diastereoisomers (*ca. syn:anti* 14:86). Spectral data in agreement with data reported earlier for compound (102).

Compounds (116) and (120): inseparable yellow oil; ν_{max} ($CHCl_3$) 3580, 3460 (OH), 2930, 1730, 1650 cm^{-1}. The n.m.r. spectral data were separated as follows: Compound (120) δ_H ($CDCl_3$) 0.99 (9H, s, *t*-Bu), 2.50 (1H, bs, OH), 3.24 (2H, d, J = 2.0 Hz, H-2), 4.01 (1H, d, J = 1.0 Hz, H-5), 5.41 (1H, td, J = 2.0, 1.0 Hz, H-3); δ_C ($CDCl_3$) 26.3 (*t*-Bu), 33.5 (C-2), 35.1 (C-6), 76.0 (C-5), 101.2 (C-3), 156.7 (C-4), 176.2 (C-1). Compound (116) (single isomer by n.m.r. analysis); δ_H ($CDCl_3$) 0.94 (9H, s, *t*-Bu), 0.99 (9H, s, *t*-Bu), 2.50 [1H, bs, 2(OH)], 3.59 (1H, d, J = 5.0 Hz, H-5), 4.26 (1H, s, H-7), 5.08 (1H, m, H-4), 7.40 (1H, s, H-3); δ_C ($CDCl_3$) 25.3 (*t*-Bu), 26.4 (*t*-Bu), 34.0 (C-8), 36.0 (C-6), 74.7 (C-7), 79.2 (C-5), 82.5 (C-4), 135.2 (C-2), 149.8 (C-3), 173.5 (C-1).

Reaction between the lithium dienolate of but-2-en-4-olide (2) and 2-methylpropanal.-Starting with but-2-en-4-olide (2) (0.72 cm^3, 10.0 mmol), 2-methylpropanal (1.00 cm^3, 11.0 mmol) and following the general experimental procedure for LDA-mediated reactions of (2) (reaction time 60 min), a dark-orange oil (1.05 g) was obtained after work-up as before. The oil was subjected

to column chromatography [silica gel, petrol-EtOAc (2:1 → 1:3)]. Spectral analysis of the column fractions indicated that the crude mixture consisted of a diastereoisomeric mixture of *4-(1'-hydroxy-2'-methylpropyl)but-2-en-4-olide* (101) (74% of crude mixture, *anti:syn* ratio 95:5 by ^{1}H n.m.r. analysis) and a diastereomeric mixture of *2,4-di(1'-hydroxy-2'-methyl)but-2-en-4-olide* (117) (26% of crude mixture, *ca.* 60:40 mixture of stereoisomers), together with trace amounts of uncharacterised polymeric material.

Spectral data on products:

Compound (101): yellow oil, spectral data commensurate with data reported earlier for (101).

Compound (117): yellow oil (impure); ν_{max} ($CHCl_3$) 3580, 3450 (OH), 1730 (CO), 1590, 1150, 820 cm^{-1}; δ_H ($CDCl_3$) major isomer 1.02 [6H, d, J = 7.0 Hz, 2(Me)], 1.05 [6H, d, J = 7.0 Hz, 2(Me)], 1.88 (1H, m, H-6), 2.05 (1H, m, H-8), 3.55 (1H, m, H-5), 3.44 [2H, bs, 2(OH)], 4.26 (1H, m, H-7), 5.00 (1H, dt, J = 6.0, 1.5 Hz, H-4), 7.43 (1H, s, H-3), minor isomer as above, except 3.40 (1H, m, H-5), 4.93 (1H, m, H-4), 7.39 (1H, s, H-3); δ_C ($CDCl_3$) major isomer 16.6, 17.9, 18.9, 18.8 [4(Me)], 32.1 (C-8), 32.4 (C-6), 72.1 (C-7), 76.1 (C-5), 82.8 (C-4), 136.5 (C-2), 148.2 (C-3), 173.2 (C-1), minor isomer as above, except 16.8, 18.0, 18.4, 18.8 [4(Me)], 32.2 (C-6), 71.7 (C-7), 76.2 (C-5), 82.5 (C-4), 147.4 (C-3); m/z (C.I.) mixture 229 $(M+1)^+$, 211 $(M+1-H_2O)^+$, 193 $[M+1-2(H_2O)]^+$.

Reaction between the lithium dienolate of but-2-en-4-olide (2) and propanal.-Starting with but-2-en-4-olide (2) (0.36 cm^3, 5.0 mmol), propanal (0.32 g, 5.5 mmol) and following the general experimental procedure for LDA-mediated aldol reactions of (2) (reaction time 60 min), a brown oil (0.85 g) was obtained after work-up as before. The oil was analysed by ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy and has been cautiously assigned as consisting of a mixture of *2,4-di(1'-hydroxypropyl)but-2-en-4-olide* (119) and *4-(1'-hydroxypropyl)but-2-en-4-olide* (100) in 73:27 ratio. The structural assignment and product ratio was based on the following n.m.r. data:

Compound (119): (4:3 mixture of stereoisomer by ^{1}H n.m.r. analysis); δ_H ($CDCl_3$) major isomer 0.96 (3H, t, J = 7.0 Hz, H-10), 1.04 (3H, t, J = 7.0 Hz, H-7), 1.50-1.90 (4H, m, H-6, H-9), 3.40-3.88 [3H, m, H-5 and 2(OH)], 4.44 (1H, m, H-8), 4.90 (1H, s, H-4), 7.38 (1H, s, H-3), minor

isomer as above, except 1.02 (3H, t, J = 7.0 Hz, H-7), 4.96 (1H, bs, H-4), 7.38 (1H, s, H-3); δ_C ($CDCl_3$) major isomer 9.4 (C-10), 10.1 (C-7), 26.2 (C-6), 28.4 (C-9), 67.4 (C-8), 72.6 (C-5), 84.2 (C-4), 138.6 (C-2), 146.2 (C-3), 172.8 (C-1), minor isomer 9.5 (C-10), 10.0 (C-7), 26.0 (C-6), 28.0 (C-9), 68.1 (C-8), 72.7 (C-5), 84.1 (C-4), 138.0 (C-2), 146.9 (C-3), 172.7 (C-1).

Compound (100): (diastereomeric mixture, *syn*:*anti* ratio 2:3 by ^1H n.m.r. analysis) spectral data in agreement with data reported earlier for (100).

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APPENDIX

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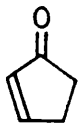
REGIO- AND DIASTEREOSELECTIVITY IN ALDOL REACTIONS OF CYCLOPENT-2-ENONE, 2-(5H)FURANONE AND THEIR DERIVED TRIMETHYLSILYLOXYDIENES

David W. Brown, Malcolm M. Campbell, Anthony P. Taylor and Xiao-an Zhang,
School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY.

Summary: Differences in erythro/threo-selectivity were assessed for aldol condensations of aldehydes with the lithium salts of cyclopent-2-enone,2-(5H)furanone, and for Lewis acid catalysed condensations with the derived trimethylsilyoxydienes.

Aldol reactions of the anion from cyclopentenone (1) have not been systematically assessed. Earlier studies showed that lithium diisopropylamide mediated alkylations were problematical,[1] and suggested that a 3-substituent was desirable for the avoidance of self-condensation processes. We therefore report further studies of the parent system (1) and the derived trimethylsilyloxy diene (2), together with interesting comparisons and differences from the chemistry of (3) and its silyl ether (4).



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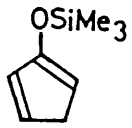

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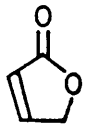

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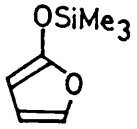

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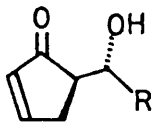
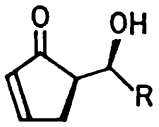


(5a) R = Me
(5b) R = Et
(5c) R = ^{i}Pr
(5d) R = $PhCH_2$
(5e) R = $C_{10}H_{21}$



(6a)
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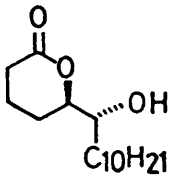

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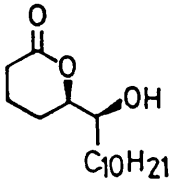

(8)

Footnote: The threo assignment is made in the cyclopentenone series on the basis of a staggered carbon chain backbone, where the two substituent groups have anti relationship. In the lactone series threo assignment is made by reference to threose, following the sugar conventions.

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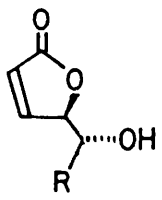
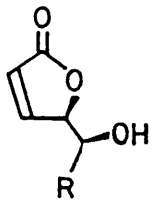
The lithium enolate of (1) (LDA,THF,-78°C) reacted with a range of aldehydes, giving threo (syn) and erythro (anti) adducts (5a)-(5e) and (6a)-(6e) in yields ranging from 70% to 85% with marked preference for the threo diastereomer (from 70:30 to 95:5, increasing with steric bulk of R.).[3] No 4-substitution was observed. Similar yields, but reversed diastereoselectivity, resulted from the zirconium enolates (LDA,$ZrCp_2Cl_2$), as observed for acyclic systems.[4]

Generally improved stereoselectivity was observed for Lewis acid catalyzed reactions of the trimethylsilyloxy diene (2).[5] A range of Lewis acids and solvents were explored and, optimally, $TiCl_4$/THF gave > 90% threo preference with, for example, 2-phenylethanal and 2-methylpropanal, although at the expense of total yield (50%).[2] This stereoselectivity is in accord with postulated transition states for silyl enolates,[6] with R 'exo' to the silyloxycyclopentadiene. [Note that no reaction could be induced by $Eu(fod)_3$ or $Pr(fod)_3$, in contrast to reactions of (4) which will be described] The threo preference was established by n.m.r. (δ CHOH 3.7,J=8Hz for threo; δ CHOH 4.2,J=2Hz for erythro)[7] and confirmed by reduction of (5a) and (6a) to known cyclopentanones.[7,8] Reversal of diastereoselectivity resulted when t-butylammonium fluoride was used to liberate the anion, giving typically a 20: 80 threo/erythro mixture.[9]

When (5e) and (6e) were catalytically reduced, and the resultant cyclopentanones subjected to Baeyer-Villiger reaction, the 6-hydroxyalkyl lactones (7) and (8) were isolated in good yields, the latter being related to a known mosquito attractant pheremone.[10] A facile route to such δ-lactones is thus apparent.



(9a) R = Me
(9b) R = Et
(9c) R = ^{i}Pr
(9d) R = $PhCH_2$
(9e) R = $C_{10}H_{21}$



(10a)
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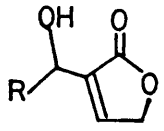

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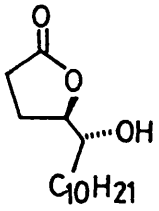

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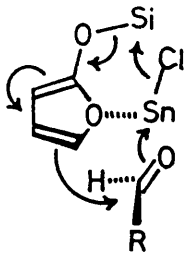

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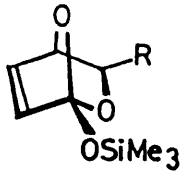

(14)

Interesting comparisons emerged from the corresponding chemistry of 2-(5H)furanone (3) and the derived silyloxydiene (4).[11] Again, these systems have received surprisingly little attention in synthesis,[12] and, in particular regioselectivity and diastereoselectivity have not systematically been explored.

The lithium enolate of (3) (LDA,THF,-78°) reacted with aldehydes to give a mixture of the γ-adducts (9a)-(9e) and (10a)-(10e), together with α-adducts (11), typically in a 1:1:6 ratio. Thus, no significant selectivity was achieved. However, silyloxyfuran (4) reacted with aldehydes in the presence of an extensive range of Lewis acids, the optimal conditions ($SnCl_4$,THF,-78°) affording threo/erythro ratios of 88:12. (In this series, threo is R,R/S,S). It should be noted that fluoride-initiated aldol reactions, although switching the selectivity, did not adequately discriminate between the diastereomers.) Initial assignments came from n.m.r. analysis of coupling constants, and lanthanide-induced shifts. More direct assignment was made by synthesizing a known precursor of the pheremone dispalure.[13] Thus, reactions of (4) with undecanal, and chromatographic separation of the major isomer (threo) gave racemic (9e) which was reduced (H_2,Pd-C) to give 5-hydroxyalkyl γ-lactone (12), spectroscopically identical to the dispalure intermediate. A general route to such γ-lactones, complementing that for the homologous δ-lactones described above, is thus exemplified.

Mechanistically, two explanations are possible for the threo selectivity. Firstly, a novel tricyclic chelate (13) may be invoked. In a concerted process the aldehyde is delivered to the 5-position, with R exo to give the threo products (9). This contrasts with the reaction of (2) in which the methylene group cannot thus be involved. A second mechanism recognises the fact that silyloxybutadienes, catalysed by lanthanides, give Diels Alder adducts.[14] Thus (4) could, via exo adduct (14), lead to threo products (9). Intermediate (14) could not be detected by direct n.m.r. monitoring of the reaction leading to (9a) and (10a), but this does not preclude the route. Interestingly, however, under the Danishefsky conditions[14] [$Eu(fod)_3$,0.5 mol%,$CHCl_3$,RT] no Diels Alder adduct was observed, but a change in regioselectivity of the aldol reaction occurred and good yields of α-adduct (11) were obtained, possibly in consequence of an alternative transition state leading to 2-(3H) furanone adducts and thence (11). Similar regioselectivity was observed for $Pr(fod)_3$.

In summary, 5-lithiocyclopentenone and trimethylsilyloxycyclopentadiene/$TiCl_4$ give predominantly threo 5-hydroxyalkylcyclopent-2-enone aldol adducts although reversal of diastereoselectivity can be achieved from the zirconium enolates or by fluoride-mediated reaction of the silyl enolate. In comparison, 2-trimethylsilyloxyfuran/$SnCl_4$ gives threo 5-hydroxyalkyl 2-(5H)furanones which are the γ-aldol adducts. These products are convertible, respectively, into threo 6-hydroxyalkyl δ-lactones (8) and threo 5-hydroxyalkyl γ-lactones (12).

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2. Yield refers to total diastereomers in the reaction as analysed by g.l.c., using internal standard. Isolated yield (medium pressure column chromatography) gave, typically, 30-50% of total separated diastereomers.

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